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GENERALIZED INTESTINAL POLYPOSIS AND MELANIN SPOTS OF THE ORAL MUCOSA, LIPS AND DIGITS (Concluded)*

A Syndrome of Diagnostic Significance

HAROLD JEGHERS, M.D.,† VICTOR A. MCKUSICK, M.D.,‡ AND KERMIT H. KATZ, M.D.§

WASHINGTON, D. C., BALTIMORE, MARYLAND, AND BOSTON, MASSACHUSETTS

DISCUSSION

Table 2 and 3 summarize data concerning our 10 proved cases of intestinal polyposis that manifested a distinctive variety of melanin spots of the oral mucosa, lips and digits.

The ages of these 10 patients ranged from nine to thirty-nine at the time of death or first study by us. In each case, however, symptomatology referable to the intestinal polyposis had been present before, usually beginning in the teens. The patients of Peutz[7, 10] and the one of Touraine and Couder[17, 18] were in an age range similar to that in our series. Apparently, the type of intestinal polyposis present in this condition becomes clinically manifest early in life.

Seven of our 10 patients were females; Peutz[7, 10] had 5 cases in males and 2 in females. The patient of Touraine and Couder[17, 18] was a male. For those with the entire syndrome the sexes were equally distributed. The sex was given for 24 cases of the pigment part of the syndrome as 11 males and 13 females.[18] Apparently, then, the same sex distribution holds also for the patients with the pigment picture alone.

A rather wide ethnologic spread is evidenced by its occurrence in persons of American, French-Italian, French, Welsh, Italian, Indo-European, Dutch and Negro family background. There are also suspected cases in English and German persons.

All our patients were of dark complexion as evidenced by brown, dark-brown or black hair and brown irides. Two had dark-blue irides. One was a lightly pigmented Negro boy. This type of complexion occurred also in the cases of Peutz[7, 10] and Touraine and Couder,[17, 18] as evidenced by either their statement or by the photographs they published.

The consistency of this in all subjects may be of significance, particularly since the pigmentary

TABLE 2. *Characteristics of the Pigmentation in Proved Cases of Polyposis.*

Case No.	Relative Intensity of Pigment Spots					Pigmentation Elsewhere on Skin	Color of Hair	Color of Iris	Age at Which Pigmentation Was First Noted
	Mouth	Lips	Fingers	Toes	Face				
1	++++	++++	++	+	++	0	Dark brown	Brown	Early childhood
2	++++	+++	+++	+	+++	0	Black	Dark brown	Early childhood
3	++++	++	?	?	?	0	?	?	?
4	++++	++	+	+	+	0	Dark brown	Dark brown	Early in life
5	++++	++++	?	?	+	0	Dark brown	Dark brown	From infancy
6	++++	++++	++	0*	+	Light, generalized negroid pigmentation	Black	Dark brown	From birth
7	++++	++	++	+	+	0	Dark brown	Dark brown	From birth
8	++	+++	+	0	+	0	Dark brown	Dark blue	From infancy
9	+++	+++	+	0	+	0	Dark brown	Dark brown	From infancy
10	++	++	+	0	0	0	Dark brown	Dark blue	From infancy

*Pigmentation present on sole of left foot.

*From the Fifth and Sixth (Boston University) Medical Services, Boston City Hospital, and the Department of Medicine, Boston University School of Medicine; the Medical Clinic, Johns Hopkins University and Hospital; and the Department of Medicine, Georgetown University School of Medicine.

†Director and professor, Department of Medicine, Georgetown University School of Medicine; physician-in-chief, Georgetown University Hospital; consulting physician, Boston City Hospital.

‡Assistant in medicine, Johns Hopkins University School of Medicine.

§Assistant director, Fifth and Sixth (Boston University) Medical Services, Boston City Hospital; assistant professor of medicine, Boston University School of Medicine.

anomaly of freckles (ephelides) is common in persons of light complexion with blond, light-brown or red hair and lighter-colored irides.

Pigmentation

In each case in which data were available pigmentation had been present from early in childhood to the age of twenty or more, with little or no change over the years and no very striking tendency to fade prior to that time. In Case 6 the mother noted the pigment at birth, and in Case 7 it was noted in a picture taken at the age of three months. Peutz[10] observed it in the second year of life. He believes that the mouth pigmentation persists but that some fading of the portion on the face may occur after the age of twenty-five. If only the mucosal portion of the pigmentation remains in the later years of life, it appears that the mucosal pattern is the *sine qua non* of the pigmentary part of the syndrome. Diminution of the facial portion of the pigmentation with the years may account for the difficulty that some patients had in recalling whether or not their ancestors had shown the pigmentary syndrome. Mucosal and even labial pigmentation is readily overlooked by the layman and, for that matter, in the average medical examination.

The most impressive feature in these cases was the consistent and peculiar distribution of their pigmentation. It was most striking on the lips and buccal mucosa, presenting as round, oval or irregular patches of brown or occasionally almost black pigment. A few patches may appear blue and probably represent the scattering phenomenon described by Edwards and Duntley[24] as being due to reflection of blue rays and absorption of red rays of the spectrum when white light is reflected from pigment particles in the dermis or corium. The patches on the lips and buccal mucosa varied from 1 mm. in diameter up to 5 mm. or slightly larger. Patches in the mouth were most prominent on the buccal mucosa, occasionally on the gums or hard palate and only rarely on the tongue. Those on the lips were more noticeable on the dental than outer aspect and more numerous on the lower than upper lip (Fig. 1, 2, 5, 6, 7, 9, 11 and 16).

Some of the spots had a somewhat stippled appearance when examined by means of a high-power magnifying glass. This phenomenon was present in all cases when looked for (that is, Case 7, 8, 9 and 10). It is of interest that the histologic study of the lesion revealed the pigment deposit to be distributed in vertical bands through the epidermis.

Biopsy of a typical pigmented spot in Case 6 was studied histologically by Dr. Lloyd W. Ketron,[25] who made the following remarks on the sections*:

> A biopsy has been taken of a pigmented macule on the hypothenar portion of the right palm. The tissue was fixed in formalin and sections stained with hematoxylin and eosin, polychrome and methylene blue and by Giemsa's method. The patient would not permit the removal of adequate tissue to make it possible to perform silver nitrate stains.
>
> Although clinically the pigmentation seems to have a uniform and diffuse distribution, the sections reveal that the changes occur mainly in vertical bands (see Fig. 18). In these segments the following alterations are seen in the various layers: in the stratum corneum there are masses of melanin conforming in size and shape with those of cells in most instances; in the basal layer there is an increased number of "clear cells" of Masson and perhaps also of the melanoblasts although none of the stains used demonstrate well the branching processes of these cells. Occasionally, one of the rete cells shows melanin granules, and a few cells in the granular layer have yellowish-brown granules. In the cutis there are a moderate number of chromatophores and occasional extracellular accumulations of melanin. One gains the impression that there is slight proliferation of the fixed tissue cells around the superficial blood vessels, which also appear to be dilated. However, because of regional differences this cannot be said with absolute certainty. These changes are similar pathologically to those seen in lentigines. However, because of the age incidence and anatomic distribution, I should hesitate to place them in that group.
>
> *Published here with Dr. Ketron's permission.

TABLE 3. *General Information and Characteristics of the Polyposis.*

Case No.	Age	Sex	Nationality	Family History		Malignant Degeneration of Polyps	No. of Operations for Intussusception of Small Intestine	Location of Polyps			Polyposis Demonstrated	
				Polyposis	Melanin spots			Stomach	Small intestine	Large intestine	At operation	At autopsy
	yr.											
1	14	F	American	*	*	0	3	Present	Present	Present	Yes	Yes
2	39	F	French-Italian	Yes	Yes	0	1	Present	Present	Present	Yes	Yes
3	17	F	American	*	*	Present	4	Present	Present	Present	Yes	†
4	30	F	Italian	Yes	Yes	*	1	*	Present	*	Yes	†
5	9	F	Italian	Yes	Yes	0	1	Present	Present	Present	Yes	Yes
6	15	M	American (Negro)	*	*	0	3	*	Present	Present	Yes	†
7	15	F	American	*	*	0	2	Present	Present	Present	Yes	†
8	27	M	American	Yes	Yes	0	3	*	Present	*	Yes	†
9	24	F	American	Yes	Yes	0	1	*	Present	*	Yes	†
10	28	M	American	Yes	Yes	0	1	*	Present	*	Yes	†

*Not specifically searched for.
†Patient living.

The above description is essentially what was noted by Touraine and Couder[18] and by Siemens[12] in the study of biopsies of pigment spots in their cases. However, the vertical bands of pigment noted in our cases were not mentioned in their reports.

One patient (Case 7) had a few small pigment spots on the mucous membrane inside the nose. None of our cases had melanosis coli as evidenced by negative examination by sigmoidoscopy or inspection of the colonic mucosa in operative or autopsy specimens. However, one of Peutz's patients had pigmentation of the rectal mucosa, first noted at the age of four.

To some degree pigment spots were noticed on the face in nine subjects. There are certain distinctive features. In contrast to the mucosal spots, those on the face are usually quite small (1 mm. in diameter or less) and are round and flat with the surface of the skin. The spots are distributed so as to be most numerous about the mouth, in some cases below the nose, about the eyes and more rarely in a butterfly pattern over the bridge of the nose. In other words they are most numerous near the orifices of the face (that is, the eyes, the nostrils and especially the lips). The spots become progressively more sparse on the forehead, temples, glabella and angles of the jaw and in the front of the ears, or, in other words, in the areas removed from the oral and nasal orifices. The facial spots usually have a darker color than freckles, and are more distinctly outlined with no tendency to coalesce as a rule. Peutz[10] has been able to follow one family for thirty years and noted a tendency for the facial spots to fade progressively after the age of twenty-five, although the mucosal spots were found to persist unchanged. Facial spots in our cases varied from minimal (Case 7, Fig. 9), to moderate involvement (Case 2, Fig. 1). None showed the marked involvement noted in the cases of Peutz[7, 10] (Fig. 14) and Touraine and Couder[17, 18] (Fig. 16). Apparently, the facial distribution of the pigmentary portion of the syndrome is most varied, is not the essential portion, and may be absent or disappear as the person gets older.

When the spots were carefully looked for, each patient showed some pigmented areas on the fingers and in some cases on the toes also. To a lesser degree a few patients had spots on the hands and feet as well. On the hands the pigment spots were most numerous on the fingers, varying from a few to many, involving both the plantar and the dorsal surface. They varied in size from 1 mm. to several millimeters in diameter, and were sometimes round and sometimes irregular in shape. As on the face and mucous membranes they were flat. In color they were light to very dark brown. The spots are particularly well depicted in the left hand of Case 2 (Fig. 2). On clinical inspection they were much more evident than is apparent in the photographs, being obscured by high lights in some pictures.

In no case was any pigment spot elevated, vascular or hairy. In addition an important observation is that no patient showed pigmentation on any part of the body in addition to the areas noted. There was no diffuse skin pigmentation, and no accentuation of pigment in the body folds or about the nipples.

The possibility that the pigment portion of this syndrome represents ephelides (freckles) must be considered. There is much against this idea. Freckles are due to inherited aggregates of melanoblasts in the skin producing sharply demarcated

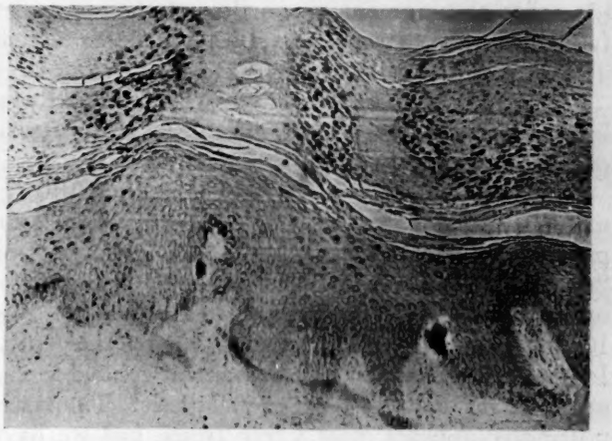

FIGURE 18. *Histologic Appearance of Melanin Spot in the Skin Obtained by Biopsy in Case 6.*

Study of this section revealed that pigment particles in the epidermis occur mainly in vertical bands. Clinically, some of the spots had a somewhat stippled appearance under magnification, which could be explained by this curious histologic pattern.

yellowish-brown areas, of varying size, and often zigzag in outline. They are more obvious in spring and summer, appear early in life but not in infancy, never occur on the palms and soles, are prominent on the exposed portion of the body and are most likely to occur in persons of light complexion.

On the face, freckles are most numerous over the nose and cheeks and most sparse near the mouth and nostrils. In other words, the distribution pattern of freckles on the face is the reverse of the pattern we have described. In fact, Siemens[12] characterized the spots of the syndrome under consideration as "ephilides inversae" because of this contrast in distribution when compared with ephelides.

The most important point against ephelides is the striking and constant occurrence on the lips and buccal mucosa even when the spots are minimal on the face. During the past few years we have examined the lips and oral mucosa of several dozen heavily freckled persons of both sexes and various age groups from childhood up through the third

decade. One was a boy who had won a "freckle contest." Although heavily freckled persons may show a few lesions on the lips, in no case did we see pigment spots on the buccal mucosa, hard palate or gums.

Lentigo is essentially a localized macular area of hyperpigmentation[26] containing a normal number of melanoblasts. They are usually multiple, dark brown, of varying size and up to 1 cm. in diameter, occurring on the covered parts of the body as well as on the face and hands and appearing later in life than freckles do. They have no characteristic or fixed pattern of distribution. There is no known hereditary predisposition. Mucous-membrane lesions do not occur. The usually accepted description and definition of lentigo seems to exclude the idea that the pigmentary portion of the syndrome falls into this category in spite of the fact that Touraine and Couder[18] refer to them as such.

Chloasma, xeroderma pigmentosa, von Recklinghausen's disease and melanosis of external origin are readily excluded from consideration.

The pigment of this syndrome is undoubtedly melanin. It may well fit into the group of melanin pigments classified by Becker and Obermayer[27] as "melanosis associated with increased number of melanoblasts." Its hereditary tendency (See Fig. 10, 12, 13 and 15) is best explained on this basis. Is the pigment syndrome a variant of ephelides or a separate and distinct form of melanosis? The latter possibility appears most likely to us, but we have been unable to prove or disprove this thesis. In essence, the nature of the pigmentary anomaly remains obscure. Apparently, it is limited to, or most common in, persons of dark complexion.

A summary of the data concerning the pigmentation is given in Table 2.

Intestinal Polyposis

The other portion of the syndrome consists of intestinal polyposis. Apparently, in each case the polyps are distributed throughout the entire intestinal tract with their most striking clinical manifestations in the small intestine.

The features referable to the polyposis in our 10 cases are given in Table 3. The presence and nature of the polyps in each subject were definitely established by means of one or more operations on the small bowel in all cases, and in addition by postmortem examination in 3 cases.

The symptomatology of these patients was referable chiefly to the small intestine with numerous episodes of abdominal pain and signs of minor obstruction terminating in one or more attacks of small-bowel intussusception. Surgery of the small intestine was performed on these 10 patients, varying from one to four operations each. Several patients had melena of varying degree. In Case 1 a sprue-like syndrome developed after resection of portions of the small intestine; the procedure led to inanition and contributed to her death.

By contrast, rectal and large-bowel symptoms and signs were minimal or absent. One patient (Case 6) had significant trouble with rectal polyps, but this disappeared after the age of four, several local operations for removal of the lesions having been performed.

Just as the symptomatology pointed to the small intestine principally, operation and autopsy revealed the majority of the polyps to be located in the small intestine in all 10 cases. Furthermore, of the small intestine, it was principally the jejunum that was involved. Peutz[7, 10] had a similar experience with polyposis involving predominantly, but not exclusively, the small intestine in his 7 cases. Four of Peutz's patients had nasal polyposis, and 1 bladder polyposis. Touraine and Couder's[18] patient was said to have only rectal polyps, but adequate small-bowel studies were apparently not done.

Although predominant in the small intestine, polyposis was also present in the stomach and colon in the 3 autopsied cases in our series. Polyps were demonstrated in the colon of 3 of the living patients and in the stomach of 1. Their presence or absence in the colon and stomach of the other patients was not demonstrated. It appears that the polyposis is present throughout the entire intestinal tract but most prominent in the small intestine.

The intestinal lesions were the usual adenomatous polyps as evidenced by histologic study of resected or autopsy specimens, or both, in all 10 of our cases. This was true also of the cases of Peutz,[7, 10] Foster[15, 16] and van Dijk and Oudendal[14] and of the rectal polyp described by Touraine and Couder.[17, 18] A representative gross lesion of the small intestine from one of our patients (Case 7) is shown elsewhere.[28] In summary, then, the intestinal polyposis in these patients appears grossly and microscopically similar to generalized intestinal polyposis in persons not having the associated pigmentary syndrome.

The well known tendency for multiple polyposis of the colon to develop malignancy apparently holds to some degree for the small-bowel polyps in cases of this syndrome. In 1 patient (Case 3) in this series, 2 of Peutz's 7 patients and possibly 3 of Foster's the small-bowel lesion became malignant. The incidence of cancer here is not so great as that in the hereditary large-bowel polyposis but is distinctive enough nevertheless.

Most of the cases of multiple intestinal polyposis described in the literature[29-33] appear to have been limited to the colon or rectum, or both. Symptomatology in these cases is rectal or colonic. It is quite rare to find any mention at all of lesions in the small intestine in these reports. Since exploratory procedures were commonly performed, any

small-bowel polyps present would probably have been found and comment made about them.

Ladd and Gross[34] studied the records of 92 cases of intestinal polyposis at Children's Hospital in Boston. In only 2 of these were polyps noted in the small intestine. At the Mayo Clinic, Coffey,[35] in a study of 29 cases of multiple intestinal polyposis, noted their localization to the colon in all but 2, in which the polyps were disseminated throughout the stomach and entire intestinal tract. Apparently, multiple polyps of the small intestine are quite rare as contrasted with multiple polyposis of the large intestine. On the basis of 7000 consecutive autopsies at the Cook County Hospital, Lawrence[36] concluded that polyps are approximately twelve times more common in the colon than in the small intestine.

In contrast to the numerous papers dealing with polyposis of the colon and rectum is the distinct paucity of studies referable to multiple polyposis of the small intestine,[37-40] especially cases with a heredofamilial pattern similar to that in colonic polyposis.[14, 15, 41] The recent review by Ravitch[28] on polyposis of the small intestine and polyposis of the entire gastrointestinal tract further confirms the rarity of these two varieties.

Our 10 cases, most of which were heredofamilial, seem a large number in view of the rarity with which such cases are described in the literature. Peutz's[7, 10] 7 similar cases makes the number even more impressive. The additional fact that each member of this relatively large group with this unusual intestinal lesion showed a peculiar and distinctive type of pigmentation seems to us to indicate that the association is not fortuitous but of real diagnostic significance.

We have not found any report with adequate bowel studies in which the pigmentation portion of the syndrome was associated solely with large-bowel polyposis. A number of surgeons with extensive experience with large-bowel polyposis, with whom this subject was discussed, were unable to recall a personally recognized example.

*Heredity**

It is well established that multiple polyposis of the large intestine is frequently hereditary. Dukes,[42] in an exhaustive review of the subject, concludes that it "is an inheritable disease which is transmitted by both males and females, that both males and females suffer from the disease and that the inheritance can be traced through several generations." Gates[43] reviewed the genetic aspects of polyposis of the large intestine and was able to discover the pedigree of a total of forty families in the literature. He concluded that the condition is a simple mendelian dominant with an occasional skip in some families.

*We are indebted to Dr. Bentley Glass, of the Department of Biology, Johns Hopkins University, for his assistance in the preparation of this portion of the manuscript.

As pointed out above, multiple polyposis of the small intestine or of the entire gastrointestinal tract, as seen in the syndrome discussed in this paper, appears to be an entity distinct from the more common colonic polyposis; yet our data indicate that it follows a similar genetic pattern. That this type of polyposis is likewise often hereditary there can be little question. Among our 10 cases, two families are represented by 3 cases each. In the literature there are no genealogic charts large enough to permit any conclusion regarding genetics. There are, however, reports of several families in which more than one member suffered from polyposis of the small intestine.[7, 14, 15, 41, 44, 45]

That the pigmentary portion of this syndrome is likewise hereditary is inescapable from the two family groups among our 10 cases, and from the fact that Touraine and Couder,[18] in reviewing the literature on the pigmentary anomaly alone, found 31 cases, of which 22 were familial. These authors presented several genealogic charts of the pigmentary anomaly indicating inheritance as a simple mendelian dominant.

Our genealogic tables of the Dutch family (Fig. 13), the Welsh family (Fig. 15), the Boston family (Fig. 12) and the Harrisburg family (Fig. 10) not only offer proof of the hereditary nature of the complete syndrome but also permit certain other conclusions.

In the first place the syndrome appears to be inherited as a simple mendelian dominant. The involvement rate of approximately 50 per cent in the second and third generations of the Dutch family, and in the second generation of the Harrisburg family, is consistent with, although not absolute proof of, such an inheritance through the mating of persons heterozygotic for this characteristic with persons not carrying this trait. In favor of inheritance of the syndrome as a dominant is the fact that, although rare, it occurs in a large percentage of members of tainted families.

Secondly, from these four charts, the characteristics constituting the syndrome appear to have a high degree of penetrance, occurring probably in the majority of those who carry the necessary factors.

Thirdly, there are no generation skips. Both males and females carry the factor, and both are affected about equally.

Further study of the genealogic tables (Fig. 12 and 13) impresses one with the fact that whenever patients were actually examined and subjected to complete studies, the full syndrome, polyposis and spots, occurred together in the same person. "Gene linkage" (that is, the presence on the same chromosome of a separate gene for each characteristic) will not explain the association. Snyder[46] states it thus:

The occurrence of genetic linkage between the genes for two traits does not change the association for these traits in the population from what it would be if they were not linked. Stated inversely, a correlation between two traits in a free-breeding population does not indicate genetic linkage between the genes for these traits.

The correct explanation for this syndrome as for the majority of the other hereditary syndromes must be the presence of a single pleiotropic gene responsible for both characteristics, the polyps and the spots.[47]

We still await the autopsy report of a patient with the characteristic pigmentation that shows absolutely no polyps of the intestine on careful search. That the converse situation occurs seems probable. There may be several reasons for the occurrence of generalized intestinal polyposis or of polyps of the small intestine without spots. First, it must be appreciated that clinical identity does not necessarily mean genetic identity; 2 cases of polyposis clinically identical may have quite different genetic backgrounds. Secondly, in other inherited syndromes, such as Marfan's arachnodactylia, essential familial xanthomatosis and von Recklinghausen's disease, there may be in the same family great variability in the completeness or degree of expression of the individual characteristics, because of factors not well understood. That variability may, at times, be present in this syndrome, although we have no definite evidence of it. It might be subsequently demonstrated that in the same family some members show only polyposis, and some only spots.

Summary

On the basis of 10 cases studied, an attempt is made to establish a syndrome that previously was not clearly identified in the English medical literature and recognized to only a very limited extent elsewhere. By supplementing our own cases with those discovered in a search of the literature and with data from personal communications, it has been possible to assemble a total of 22 proved, 5 probable and 4 possible cases.

This syndrome consists of two features: distinctive melanin spots of the buccal mucosa and lips — the face and digits may be involved to a variable extent, but the mouth pigmentation is the *sine qua non* of this portion of the syndrome; and polyposis (synonyms are adenomatosis and papillomatosis) of the small intestine. The stomach, colon and rectum may be involved, but the presence of polyps in the small intestine is the constant feature of this portion of the syndrome.

Our group of 10 cases included 6 in which more than one member of the same family was involved. Sufficient genealogic data are reported to demonstrate the hereditary nature of the syndrome, which appears to be inherited as a simple mendelian dominant. Sporadic cases also occur.

The syndrome appears to have important diagnostic significance in that the external manifestations may be of considerable value in the recognition of the intestinal condition.

As a result of several lectures on this subject, 3 additional cases have been called to our attention since the preparation of the manuscript. Two were examined in detail by one of us — 1 through the courtesy of Dr. C. Stuart Welch of the Joseph H. Pratt Diagnostic Hospital, Boston, and the other through the courtesy of the staff of the United States Naval Hospital, N.N.M.C., Bethesda, Maryland. (A colored illustration of the latter case was reproduced with the first section of this report.) All 3 patients had small-bowel polyposis, one or more operations for intussusception of the small intestine and the typically distinctive melanin spots. The last 2 cases will be reported separately by the institutions mentioned above. These additional cases provide further evidence that the syndrome is a distinct entity.

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AUREOMYCIN TREATMENT OF HERPES ZOSTER*

MAXWELL FINLAND, M.D.,† EDMUND F. FINNERTY, JR., M.D.,‡ HARVEY S. COLLINS, M.D.,§ JOHN W. BAIRD, M.D.,¶ THOMAS M. GOCKE, M.D.,|| AND EDWARD H. KASS, PH.D., M.D.,**

BOSTON

AUREOMYCIN and Chloromycetin are generally referred to as agents that are effective against "viral" infections. Their demonstrated therapeutic action in this field, however, has been limited to rickettsial diseases[1-17] and to infections with the psittacosis-lymphogranuloma venereum group.[1, 4, 17-21] Aureomycin has also proved efficacious in cases of the so-called viral or primary atypical pneumonias.[22-25] The etiology of the latter is still unknown beyond the demonstration that some of them may be transmissible by filtrates of materials from human cases.[26, 27] Neither of these agents has yet been proved to be effective against what might be called true viruses, such as those which cause yellow fever, influenza, poliomyelitis or the encephalitides.

Recently, some beneficial effects have been claimed for these antibiotics in certain skin diseases that are thought to be due to viral agents,[28-32] among which is herpes zoster.[31, 32] As regards the etiology of the latter, grafts of human skin onto the chorioallantois of chick embryos have been successfully infected with vesicle fluid from a patient with herpes zoster,[33] and elementary bodies have been demonstrated by electron microscopy in the vesicle fluid from various clinical types of herpes-zoster lesions.[34, 35] The demonstration of a therapeutic effect in this disease is therefore of considerable interest as well as of practical importance.

In this paper are presented the results of aureomycin treatment in 24 cases of herpes zoster. Although a specific therapeutic effect has not been demonstrated beyond any reasonable doubt, the results are sufficiently encouraging to warrant this report.

*From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard) and Skin Service, Boston City Hospital, and from the Department of Medicine, Harvard Medical School, and the Department of Dermatology, Tufts College Medical School.

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†Associate professor of medicine, Harvard Medical School; chief, Fourth Medical Service, Boston City Hospital; associate physician, Thorndike Memorial Laboratory, Boston City Hospital.

‡Formerly, teaching fellow in dermatology, Tufts College Medical School, and resident, Skin Service, Boston City Hospital.

§Formerly, Milton Fellow, Harvard Medical School, and research fellow, Thorndike Memorial Laboratory.

¶Teaching fellow in dermatology, Tufts College Medical School; resident, Skin Service, Boston City Hospital.

||Research fellow in medicine, Harvard Medical School and Thorndike Memorial Laboratory.

**Senior fellow in virus diseases, National Research Council; research fellow in medicine, Harvard Medical School and Thorndike Memorial Laboratory.

MATERIALS AND METHODS

Cases Treated

The 24 patients included in this report were all treated during the first nine months of 1949. All had lesions that were clinically characteristic of herpes zoster. With 4 exceptions, they were consecutive cases seen on the wards or in the Out Patient Skin Clinic of the Boston City Hospital. However, mild cases or those in which there was any doubt of the diagnosis or the activity of the disease were omitted. Of the 4 patients who were not treated at this hospital, 1 was a physician, another was the wife of a physician, and a third was a patient treated in another hospital by a dermatologic colleague. Detailed reports of these 3 cases were made by the physicians concerned.

Aureomycin. The aureomycin was supplied in the form of capsules each containing 250 mg. of the hydrochloride and was given by mouth, generally in doses of 1 gm. four times a day (after each meal and before retiring), and the individual doses were reduced to 0.5 gm. each after definite improvement occurred or if there was significant nausea or vomiting. Crystalline aureomycin hydrochloride was also supplied in sterile vials containing 100 mg. for intravenous use. This was given to 2 patients who refused oral therapy; individual doses of 500 mg. in 500 or 1000 cc. of 5 per cent dextrose were given by slow intravenous drip taking about an hour for each dose. (The recommended alkaline buffers were not used in these cases.)

CASE REPORTS

CASE 1. The patient was a retired physician whose herpetic lesions began in the right side of the back near the midline and extended within 7 to 10 days around the lower axillary region and reached almost to the midline. The eruption was very extensive posteriorly but tapered off as it spread to the front of the thorax. The patient paid little attention to his lesions until the middle of the 3rd week, when they became much worse and caused him considerable pain and discomfort. A month after the first appearance of the lesions and after failing to obtain relief from various remedies, he took aureomycin by mouth, a total of 7 gm. in 3 days, without any effect. He then took a course of x-ray therapy to the lesions over a period of 1 week. This gave slight relief from the pain, and the lesions began to improve but within a few days "the whole thing flared up again."

Because of the failure of the first course of x-ray treatment to terminate the disease, the patient was given a second course of x-ray treatments over a period of 2 weeks, during which he also took aureomycin, 1 gm. daily, in divided doses. He improved steadily, and by the end of the 2 weeks the lesions had healed, the pain had subsided and he was able to lead a normal life again. In the course of the next 4 or 5 months, however, he had occasional recurrence of sudden, sharp pains or burning sensations, each lasting about 1 or 2 minutes and limited to the region of the eruption.

In this case a short course of aureomycin given during the fifth week failed to alleviate the symptoms or prevent a relapse. The lesions and acute symptoms finally yielded by the end of the second month and after a second course of x-ray therapy together with small doses of aureomycin given over a period of two weeks. The role of aureomycin in this case cannot really be assessed. There were no untoward effects from the antibiotic.

CASE 2. One day after a "light" treatment at his barber's the patient began to have a burning sensation over his right eye. This continued for 3 days, after which herpes zoster appeared, first as patches of erythematous lesions over the right side of the forehead and then over the scalp. During the next 24 hours the lesions became deeply vesiculated in 2 patches, one over the right eyebrow and the other at the hairline, and these caused a constant, dull aching and marked itching. Aureomycin hydrochloride was started at this time, 1 gm. orally 4 times a day for a total of 12 gm., and this produced no untoward effects. No local therapy was used. On the day after this therapy was started, 12 discrete and widely scattered vesicles, each on an erythematous base, appeared over the chest and abdomen. The right upper eyelid became swollen on this day, but no new lesions appeared in this area. The cornea and bulbar conjunctiva were spared. The pain and itching stopped, and the edema subsided on the 2nd day. The original lesions became hemorrhagic and necrotic and then dried up rapidly. All lesions were completely healed within 1 week of the first dose. There was no relapse and no post-herpetic pain.

CASE 3. This patient's first symptom was prickling pain over the left eye, which was soon followed by the appearance of groups of vesicles, one on the left side of the bridge of the nose, 2 over the eyelid and another on the forehead. Erythematous macules were also scattered over the scalp. Aureomycin hydrochloride was started 48 hours after the onset of symptoms; 1 gm. was given by mouth 4 times daily for a total of 24 gm. and without untoward symptoms. No local therapy was used. On the day after the aureomycin was started the left eye was swollen shut by edema of the lids, but the cornea and conjunctiva were spared, no other new lesions appeared, and vesicles did not develop in the macular lesions over the scalp. Thereafter, improvement was rapid. The edema of the lids and the pain subsided in 2 days, and within 5 days all the lesions had cleared and there was only slight itching of the scalp during this time. There were no relapses, sequelae or pain thereafter. In this case many lesions were apparently aborted by the aureomycin.

CASE 4. The first symptom was itching, and after 1 day a group of vesicles appeared on the back of the right shoulder. During the next 7 days 5 more groups of closely packed vesicles appeared around the original lesions, and severe itching persisted. Aureomycin orally was started on the 10th day, 1 gm. 4 times daily. Because of nausea, the individual doses were reduced on the second day to 0.5 gm., and treatment was continued for a total of 5 days. No local therapy was used. Within 72 hours, most of the lesions had dried and were healing, and the itching had almost entirely subsided. When the patient was next seen 4 days later, all the lesions had completely cleared, and there had been no further itching. There were no relapses, nor did the patient later experience any pain. The dermatologist who followed this patient in the clinic noted in his record that he had never seen such a case clear so rapidly.

CASE 5. The patient first experienced marked itching, and within a few days an extensive vesicular eruption appeared over the right middle portion of the thorax from the spine around to the midline anteriorly. The lesions rapidly became gangrenous, and there was slight pain during the 3rd week. At that time the patient was admitted to the hospital, and aureomycin was started, 1 gm. being given orally 4 times a day for a total of 25 gm. There were no untoward effects. There was remarkably rapid improvement, with considerable clearing of the lesions and subsidence of pain within the first 2 days and almost complete clearing with minimal scarring within 6 days. Four days later, however, the patient began to have slight pain referred to the affected area. This pain increased in severity at first and then persisted with diminishing intensity for about 6 weeks without the appearance of any further lesions. It was difficult to evaluate the pain in this patient since he had no home and no resources and was obviously anxious to remain in the hospital as long as possible. In this case treatment with aureomycin was started late and appeared to have a strikingly beneficial effect on the skin lesion, but did not seem to prevent the appearance of postherpetic pain.

CASE 6. This patient first experienced discomfort in the left ear and cheek. On the following day she had general malaise and noted the appearance of a herpetiform eruption over the same area and also some enlarged cervical lymph nodes on that side. The symptoms and some shooting pains over the mandibular region increased, and the lesions advanced during the next 2 days until aureomycin was started and for about 16 hours longer. Thereafter there was steady improvement: the lesions cleared almost completely within 3 days, and the shooting pains rapidly diminished in intensity and then subsided entirely within 9 days. Neither of these recurred. The aureomycin was given by mouth, 1 gm. every 6 hours for 10 doses and then 0.5 gm. every 6 hours for 5 more doses. During the first 3 days, there was marked nausea for about 10 minutes after each dose, particularly when the drug was taken on an empty stomach, and during the next 2 days the nausea was continuous and there was also some diarrhea. This patient was nursing an infant during this episode, and the baby remained well.

CASE 7. The first symptom in this patient, a dental student, was a severe itching over the left flank, which caused him to scratch a good deal. On the following day the area was painful "like a boil," and during the succeeding 3 days groups of vesicles appeared lateral to the original lesions and a large patch of vesicles appeared over the upper outer quadrant of the buttock. The patient applied tincture of iodine to the initial lesion and various lotions to the entire area and also took some analgesic pills, all without preventing the progress of the lesions or of the symptoms. Aureomycin by mouth was begun on the 7th day, 1 gm. 4 times a day for 2 days, and then, because of increasing nausea and frequent loose bowel movements, the dosage was reduced to 0.5 gm. 4 times a day and continued until a total of 12.5 gm. had been given. The untoward symptoms subsided completely on the smaller dosage. The pain and itching increased during the first 24 hours, at the end of which the lesions had already begun to improve. Within 48 hours, the vesicles had almost completely dried, and the pain had subsided. On the 4th day the lesions were almost completely healed, and only slight itching persisted for another day. There were no further lesions and no recurrence of the pain.

CASE 8. The patient first noticed a "dead feeling" and some prickling in the left flank. During the next few days groups of vesicles appeared over this area and were soon followed by sharp, knife-like pain. When the patient was first seen, at the end of the 2nd week, the lesions involved an extensive area from the spine at the level of the twelfth thoracic and first lumbar segments, around the flank and to the midline anteriorly from just above the umbilicus to the groin. There were some old lesions that were beginning to dry up and many new groups of vesicles with deep surrounding erythema that had appeared during the previous 2 days. There was severe superficial prickling and some sharp pain and paresthesias over the involved areas, and also a "clutching" feeling in the abdomen. Aureomycin was begun at this time. The patient took 750 mg. by mouth 4 times a day for 3 days. No other therapy was used. No further lesions appeared after this treatment was started, and there was almost complete healing of the lesions by the end of the 3rd day. There was still slight pain at this time, but this soon subsided and there was no recurrence of pain or lesions.

CASE 9. The patient awoke one morning with a marked burning sensation over a band of the left upper portion of the chest corresponding to the cutaneous distribution of the third and fourth thoracic segments. Only after this sensation

had continued for about 5 days did he become aware of an extensive outbreak of shingles over this area. He was first seen 2 days later, when there were many groups of fresh vesicles with surrounding bright erythema. Aureomycin was started at this time, and the patient took 1 gm. 4 times daily for 3 days. On the 3rd day he felt nauseated and vomited after the last 2 doses. The pain and burning cleared rapidly, and the lesions began to dry up promptly and were entirely healed within 5 days. There were no sequelae.

CASE 10. This patient first noticed some itching and a burning sensation around the left upper eyelid, which soon became red, hot and swollen. Two days later, herpetic vesicles appeared above the eyelid and spread back over the left side of the scalp. The redness and swelling of the eyelids, especially the upper lid, increased, and some of the lesions became pustular. At that time he consulted a physician, who treated him with procaine penicillin, 2 daily injections of 300,000 units each for 2 days and 1 a day for 4 more days and then sent him into the hospital. At that time the lesions involved the left side of the nose, forehead and scalp. The eye was swollen shut and the patient's temperature was 101°F. Most of the vesicles had become pustular, some of them had become encrusted, and pus oozed from the inner canthus of the eye. The left eye was swollen shut; there were blepharitis and keratoconjunctivitis with marked clouding of the cornea, and 2 distinct herpetic lesions of the cornea were visualized with fluorescein. The white-cell count was 5600, with 88 per cent neutrophils. The blood nonprotein nitrogen was 107 mg. per 100 cc., and the urine was loaded with pus cells. Culture of the pus from the forehead yielded a predominance of hemolytic *Staphylococcus aureus* and some *Staph. albus*, alpha-hemolytic streptococci, *Proteus vulgaris* (*Bacillus proteus*) and *Clostridium perfringens* (*Cl. welchii*). A culture of pus from the left eye yielded *Escherichia coli*, *P. vulgaris* and a few staphylococci. The blood culture was negative.

The patient was treated with an aqueous solution of sodium penicillin G, 100,000 units intramuscularly every 4 hours, and sulfadiazine by mouth, 1 gm. every 4 hours. The latter was stopped after 3 days when he began to vomit and the sulfadiazine level was found to be 21.3 mg. per 100 cc. free and 26.3 mg. total. The penicillin was discontinued on the next day. During these 4 days new vesicles kept appearing, and there was no improvement. The blood nonprotein nitrogen was 85 mg. per 100 cc. Aureomycin therapy was then started, 1 gm. of the hydrochloride being given orally every 4 hours and 2 drops of fresh 1 per cent aqueous solution of aureomycin borate (50 mg. in 5 cc.) being instilled into the left conjunctival sac every 1 or 2 hours. The oral dose was reduced to 0.5 gm. every 6 hours after 5 days because of nausea and some vomiting.

Within 24 hours of the beginning of aureomycin therapy the involved areas began to look definitely less inflamed, and no new lesions appeared thereafter. The edema of the lids began to subside on the 2nd day. By the 3rd day, all redness of the skin had gone, the purulent discharge had decreased markedly, and most of the lesions had become encrusted. By the 4th day healing of the skin had definitely begun, but at this time the patient complained of pain in the eye for the first time. The cornea still looked cloudy but much less inflamed, and the 2 herpetic lesions were smaller. All the swelling of the eye had subsided after 9 days, when the aureomycin was stopped. Some pain persisted, and 2 days later there was a recurrence of the conjunctival infection and of a small amount of purulent discharge, but the corneal lesion continued to improve. A culture of the pus from the conjunctiva at this time showed *Staph. aureus* and *P. vulgaris*, the former sensitive to 50 microgm. and the latter resistant to 200 microgm. of aureomycin per cubic centimeter. The blood nonprotein nitrogen was 114 mg. per 100 cc. at this time, but there were only a few pus cells in the urinary sediment.

The patient began to vomit again after the course of aureomycin therapy, and his tongue became fiery red, smooth and shiny. This cleared promptly after treatment was stopped. He was digitalized, and fluids were given parenterally, with a careful check on electrolytes. During the following 4 weeks, without further antibiotic or chemotherapy, the eye gradually improved, and the nonprotein nitrogen dropped to near normal levels. At this time the corneal opacity had cleared almost completely and the ulcers were barely demonstrable. When the patient was last seen there was no further trace of any skin or ocular lesions. Vision was apparently unimpaired, and the conjunctivas were clear. There was no post-herpetic pain and no recurrence of lesions.

The result in this case, though not spectacular, was considered to be moderately good because of the poor prognosis that usually accompanied this type of lesion in patients of this age group.

CASE 11. The onset in this case was with pain and smarting, which was followed on the next day by the appearance of erythema and groups of vesicles scattered about the left side of the chin, jaw and temporal area. By the 3rd day, when the patient entered the hospital, some of the lesions had become bullous, and there were lesions on the left buccal mucous membrane and soft palate. Aureomycin was started on that day but was stopped because of nausea and vomiting after only 3 doses of 1 gm. each had been given. Two days later there was no improvement, and several crops of new lesions had appeared, including a few on the side of the tongue. The patient was then given 500 mg. of aureomycin hydrochloride in 500 cc. of 5 per cent dextrose solution by slow intravenous drip. On the following day the erythema was much less intense, and many of the vesicles had begun to dry. A second and similar injection was then given, and this was followed by oral doses of 0.5 gm. 4 times a day for about 7 days. Except for occasional vomiting she tolerated this dosage well, and marked improvement followed. The lesions on the tongue improved rapidly, and the skin lesions became dry and encrusted after 2 days. The lesions had all dried up and the pain subsided after 4 days. All the lesions had completely healed within 1 week. The burning sensation in the face and the tenderness of the tongue regressed slowly during this period. After discharge from the hospital, however, she began to have periodic, lancinating pains in the face, which gradually decreased in frequency and severity and finally stopped after about 2 months. After that time the site of the skin lesions was no longer discernible, but there were 2 pale, circumscribed pinkish-gray plaques without surrounding erythema on the side of the tongue.

In this case the lesions cleared, but post-herpetic pain was not prevented by the treatment.

CASE 12. Aureomycin was started in this patient as soon as she was admitted to the hospital in the middle of the 3rd week after the first appearance of her shingles. At this time there were extensive gangrenous herpetic lesions involving the right upper portion of the thorax anteriorly and posteriorly and the lower axillary region, and the patient was complaining of severe pain and burning sensations. She received 1 gm. orally 4 times a day, and because of moderate nausea and some vomiting after the second day, the individual doses were reduced to 0.5 gm. and continued for another 4 days. By the end of the 2nd day of this treatment there was remarkable drying of the lesions, no new ones had appeared, and there was only slight residual pain. Healing proceeded rapidly; the superficial ones were almost completely healed in 4 days, and the deeper ones healed during the next few days. After the patient left the hospital, however, she again had considerable burning and some intermittent shooting pains over the involved areas. For this she was given codeine and local applications of collodion by her physician. The pains gradually subsided, but the burning persisted for about 3 months. After that time there was still some faint erythema at the site of the lesions, probably maintained by the local applications and irritation.

CASE 13. The herpetic lesion first appeared in this patient on the left side of the forehead 1 week after she sustained a bump on her head. During the next few days, groups of vesicles appeared on the cheek, below the eye and on the hard palate — all on the left side. By the end of 1 week, when she entered the hospital, there was extensive edema over the entire area, with intense redness surrounding the

lesions and the left eylids were swollen. Aureomycin was started by mouth at this time, but only 2 gm. was given, and the patient rejected each of them and refused oral medication. She was then given an intravenous injection of 500 mg. of aureomycin hydrochloride. Within 24 hours, the lesions in the mouth had almost cleared, and there was considerable improvement in the facial and palatal lesions, the erythema and edema decreased markedly, and the vesicles appeared to be drying up. A second intravenous dose of 500 mg. was given at this time and the edema and pain were entirely gone by the next day, and healing of the lesions proceeded during the next 2 days. The patient refused further medication and left the hospital. New lesions then promptly began to appear and spread over the scalp and side of the face and were accompanied by severe pain and itching. The lesions of the eye also reappeared and progressed. All the lesions healed very gradually over a period of 6 weeks, leaving scars of the skin and cornea. The latter remained hazy, and the patient's vision in the affected eye remained markedly blurred after 3 months. The pain and itching also persisted, though with diminished intensity throughout this time.

In this case marked improvement followed a brief course of intravenous injection of aureomycin, and there was a prompt, severe and prolonged relapse after the aureomycin was stopped.

CASE 14.* This Negro first felt a burning sensation over the right side of the forehead, scalp and temporal region and soon noted numerous small blisters over this area. By the next day the lesions had increased in size and number, and the right eye had become red and swollen. When first seen on the 3rd day he had numerous vesicles and bullae from 1 to 13 mm. in diameter over the right side of the head involving the forehead, upper eyelid and parietal region of the scalp. The lids were swollen almost completely shut. In addition, about 30 small vesicles were scattered over the rest of the body. There was only slight pain over the affected area of the head. The temperature was 99.5°F., and the white-cell count 4100. Aureomycin by mouth, 4 gm. daily, was promptly started, and no other therapy was used.

In the course of the next 2 days the temperature rose to 103.8°F., and the eruption extended, with vesicles appearing on the side of the nose down to the lip; a few more bullae appeared on the forehead, and the eye was swollen shut. The lesions on the trunk, however, did not progress or increase. The tarsal conjunctivas were markedly injected, and there was some seropurulent discharge but the cornea and bulbar conjunctivas remained clear. On the 3rd day the maximum temperature was 99°F., the vesicle fluid remained clear, and no new lesions appeared. By the 4th day, the lesions had definitely begun to dry up, the eyelids were much less swollen and could be opened, the conjunctival injection subsided, and the cornea had remained clear. At the end of 1 week of treatment all of the lesions were solidly encrusted, and healing had definitely begun. Aureomycin was continued for 2 more days at 2 gm. a day, and healing progressed thereafter. There were no untoward effects from the aureomycin. There was no recurrence of lesions and no post-herpetic pain.

The rapid improvement in this case was considered to be quite striking considering the severity of the lesions. It was also believed that corneal involvement may have been prevented by the treatment.

CASE 15. Five days before entering the hospital this patient noticed a rash, which began as a group of reddish raised lesions on the right side of the lower abdomen and on the right flank. This was followed by the appearance of scattered papular and vesicular lesions over the trunk and extremities. The patient experienced pains down his legs, cramps and numbness in his toes and some burning over the lesions. When he was first seen he had several groups of lesions over the right flank and abdomen, including one large area that was gangrenous and pustular. There were also numerous scattered papules, vesicles and pustules and some encrusted lesions widely scattered over the extremities, trunk, face and neck. Two days later fresh clusters of herpes lesions, one of them a cluster of vesicles, 2 by 5 cm., with surrounding deep erythema, appeared in the right flank.

Aureomycin by mouth, 0.5 gm. every 4 hours, was then started and this was increased to 1 gm. every 4 hours on the 3rd and 4th days, after which the original dosage was resumed for 3 more days. The only untoward effect was slight nausea after 2 of the 1-gm. doses. The pain had subsided entirely within 2 days. There was rapid improvement in the lesions, and by the 3rd day they had dried, encrusted and cleared markedly. After 6 days, when treatment was stopped, there was almost complete healing, only a few faint erythematous patches remaining. There were no recurrences of the pains or the lesions. When the patient was last seen, only a few slightly pigmented superficial scars were visible at the site of the gangrenous lesions on the lower abdomen.

CASE 16. The first symptom in this case was pain in the right shoulder radiating down the ulnar aspect of the arm—dull and aching at first but soon becoming intermittently knife-like and severe enough to interfere with sleep. On the following day the pain was worse, involving the upper right anterior portion of the chest, with radiation around to the spine, and a herpetic rash appeared on the inner aspect of the arm. On the 3rd day vesicles and erythema were also noted on the chest and back; those on the arm had become extremely painful, and the lesions had spread over most of the ulnar surface of the arm and hand, including the fingers. On the 4th day marked erythema and vesiculation covered this area and also a band about 4 cm. wide across the chest from the angle of Louis around the lower axilla to the fourth dorsal vertebra.

Aureomycin was started by mouth at this time. The patient took 1 gm. every 4 hours, omitting only 1 night dose. After 48 hours, the pain had almost entirely subsided, and there was only a residual mild intermittent aching. There was still moderate erythema, but the vesicles had definitely begun to dry up and no new lesions appeared. Because the patient had mild diarrhea, the individual doses of aureomycin were reduced to 500 mg. each. Two days later, he was entirely free of pain, only a faint erythema was barely discernible, and there were many dry, punctate crusts over the chest and arms. There were no further untoward effects from the antibiotic, which was stopped at this time. The lesions healed rapidly, and there were no recurrences of pain or lesions.

CASE 17. The patient was being treated in the Medical Clinic with digitalis and diuretic for chronic congestive heart failure when she began one day to complain of severe pain in the left side of the chest. When she returned 2 days later, she had extensive groups of herpes vesicles, many of them bullous and each on a deeply erythematous base over an area about 8 cm. wide and extending from the spine at a level of the fourth to the sixth thoracic segment around and below the axilla to the middle portion of the chest anteriorly. There was intense pain referred to this area — severe enough to interfere with sleep.

Aureomycin, 1 gm. 4 times a day, was promptly started, and no other local or systemic treatment was used for these lesions. In the course of the next 3 days, the pain improved considerably, no new lesions appeared, and many of the vesicles had begun to dry up, but clear bullae were still present and there was still considerable deep erythema. Within the following 2 days the pain had almost completely subsided, and there was only a mild burning sensation over the lesions, which were now all covered with clean dry crusts and surrounded by some erythema. The patient had some nausea, and the dose of aureomycin was reduced to 0.5 gm. 4 times daily. After 8 days there were only a few crusted lesions with faint erythema, and all the others showed considerable healing. The patient had 2 or 3 large loose bowel movements daily and lost a considerable amount of her edema — much more than had previously been accomplished with mercurial diuretics.

*Treated on the Dermatologic Ward of the Massachusetts General Hospital and reported through the courtesy of Dr. Walter F. Lever.

Aureomycin was stopped at this time. The patient still had some slight burning sensations during the next 3 days. A week later she again began to have rather annoying twinges of pain referred to the scarred areas, but there were no new lesions or local reactions. Aureomycin treatment was resumed for 2 days, with slight reduction of the pain but without complete relief. The itching and the twinges of pain continued for 2 more weeks.

In this case there was marked and rapid improvement in the local lesion and relief from pain accompanying the aureomycin therapy during the acute phase. The late pain was not prevented, though it may have been very slightly eased by further doses of aureomycin.

CASE 18. The patient first noted a burning sensation over the lateral aspect of the right thigh, and a pale erythematous rash appeared over this area. In the course of the next 3 days, the erythema became deeper, groups of clear vesicles appeared in the erythematous area, and the burning sensation became more severe and was soon accompanied by recurrent, intense stabbing pains. By the 7th day, when he was first seen, the lesions involved the lateral aspect of the upper two thirds and part of the anterior surface of the lower third of the right thigh.

Aureomycin was promptly started and given in doses of 1.0 gm. every 4 hours, one night dose being omitted. After 2 days the pains and burning subsided almost completely, and the lesions began to dry up rapidly. On the 3rd day rather severe diarrhea, with urinary frequency and dysuria, developed. The dose of aureomycin was then reduced to 0.5 gm. every 4 hours and continued for 4 more days. The diarrhea and urinary symptoms were promptly relieved. The lesions, meanwhile, began to heal and by the end of a week were almost completely healed, leaving only faint erythematous areas. No new lesions had appeared.

On the morning after the aureomycin was stopped, the patient on arising noted that his tongue was swollen. The swelling subsided in about 2 hours, but he then began to have tenderness, itching, puffiness and redness of his hands, and his face felt flushed. He was given 25 mg. of Thephorin (an antihistaminic), and within 1 hour the lesions and swelling cleared completely and did not recur. He had no previous history of sensitivity reactions, but he had been taking codeine and barbiturates since the onset of the shingles. It is possible that these manifestations represented a sensitization reaction to the aureomycin, although a reaction to either the codeine or the barbiturates could not be excluded since the clearing of the urticaria followed the discontinuance of these drugs as well as the aureomycin.

CASE 19. The patient first noted a burning pain beginning in the middle of the back and radiating around the right axilla to the sternum, and then an erythematous rash appeared over the right breast. On the next day she had a slight headache and malaise; she felt chilly, the temperature rose to 101°F. and she was sent into the hospital. By this time the erythema had become deeper, and groups of vesicles had appeared in the erythematous areas, which now extended from the midline over the breast to the posterior axillary region. There was marked hyperesthesia over this area.

Aureomycin was started at this time and given in doses of 1.0 gm. every 4 hours for 10 days, with no untoward effect except for some nausea on the last day. Within the first 24 hours there was a decided decrease in the hyperesthesia, and by the following day there was much less erythema and the vesicles were beginning to dry up. The pain decreased in intensity over the following 2 days, but a sensation of soreness and burning in the axilla persisted for a few days longer. Meanwhile, the erythema cleared and the vesicles dried up completely and began to heal. No new lesions appeared after the aureomycin was started, and there was no late recurrence of pain.

CASE 20. The patient's wife first noticed redness over the back of his chest near the spine, and this soon extended around the right over the lower ribs to the sternum. Two days later anorexia and general malaise developed, and the temperature rose to 100°F. At this time groups of vesicles appeared in the area of erythema to which the patient applied a lotion prescribed by his physician. By the 4th day the lesions over the involved segment had increased in number, and numerous isolated lesions resembling those of chicken pox were noted over the head, trunk and extremities but the scalp, palms and soles and the mucous membranes of the mouth were spared. Accompanying the generalized eruption there was considerable itching, anorexia and a low-grade fever. The patient continued to apply lotions to the skin and took some codeine and salicylates. Pain then began insidiously and increased in intensity after the 9th day. By the end of the 2nd week the generalized rash had completely cleared and the local lesions were beginning to dry, but the pain was still severe and there were still some acute vesicular lesions.

Aureomycin was begun at this time with doses of 0.5 gm. by mouth 5 times a day and continued for 7 days. There were no ill effects except for slight nausea on several occasions. The lesions had been covered with fullers' earth by a nurse, and the healing and drying was somewhat delayed, but the pain subsided entirely within 36 hours after aureomycin was started and no new lesions appeared. Healing progressed steadily, but a slight gnawing sensation persisted for several days.

CASE 21. The patient first noted a burning sensation on the left side of his chest, and on the following day a group of erythematous lesions and some small vesicles began to appear over this region. When first seen on the 3rd day he was having intense shooting pains, and the burning sensation had become more severe. There were groups of small vesicles over deeply erythematous areas extending in a band about 6 or 7 cm. wide around the left side of the chest from the middle portion of the back to the sternum, sparing only the axillary region.

Aureomycin by mouth, 1 gm. 4 times a day, was promptly started. No new vesicles appeared after that. Within 2 days the pain had eased considerably, but there was still some slight burning sensation and hyperesthesia over the scapular region. After a week the lesions were all encrusted and dry, and there was no further pain and only a slight itching at night over the healing lesions. There were no untoward effects from the aureomycin, and no other local and systemic treatment was used.

CASE 22. This patient first noted intermittent, sharp, stabbing pains in the right axilla. These were followed in a few days by similar pains down the medial side of the arm and across the right side of the chest. By the 5th day, after the pain had become quite severe, a rash appeared in the right axilla and spread quickly. When she was first seen 3 days later, the vesicular, herpetiform rash involved the axilla, the posterior surface of the upper arm and also an area extending in a band across the chest at the level of the fourth thoracic segment — all on the right side. There were also numbness and hyperesthesia on the same side involving the little finger, triceps area and ulnar surface of the forearm to the wrist. The patient had been intimately exposed to chicken pox 2 weeks before her first symptoms had begun.

Treatment was started with 1 gm. of aureomycin by mouth 4 times daily. On the 2nd day, however, the patient reduced the individual doses to 0.5 gm. because of severe nausea. The gastric distress continued on this dosage, and she took only 0.5 gm. on the 3rd day and 250 mg. on the next day. Her first return visit was on the 5th day, when the pain had almost completely subsided. Although a few new vesicles appeared in the axilla during the 1st day of treatment, most of the lesions were dry and crusted over. Further aureomycin was prescribed, but the patient took only 1 dose of 0.5 gm. The lesions continued to heal, and there was no further pain or recurrence of lesions. When she was next seen 4 weeks later only a few faint scars were discernible.

CASE 23. The patient first noted sharp, shooting pains in the left buttock radiating along the posterior aspect of the thigh to the knee. The pains continued intermittently for 2 days, and then a vesicular rash appeared, first on the left thigh and then just above the left buttock. When he was first seen on the 3rd day there were small vesicles in clusters with surrounding erythema scattered along the lower half of the medial aspect of the left thigh, and there was one

cluster just above the patella. There were also clusters of vesicles to the left of the sacral cornu and a few early erythematous, nonvesicular lesions scattered along the upper half of the medial surface of the left leg along the margin of the gastrocnemius.

Treatment with aureomycin, 1 gm. orally 4 times a day, was begun at that time and continued for a total of 22 gm. There were no untoward effects. After 2 days of this therapy the pains were entirely gone, there was only slight itching, and the lesions were beginning to dry. The itching had completely subsided and the lesions were almost completely healed when the therapy was stopped. There were no recurrences of pain or lesions.

CASE 24. This patient first experienced severe lancinating pains, which began at about the angle of Louis and radiated around the right side of the chest. General malaise and anorexia accompanied the pain. After 4 days she noted an erythematous rash over the painful area, and she felt very weak. When she was first seen on the 6th day, she still complained of recurrent pains over the right upper portion of the thorax, but these were somewhat less severe. At this time, however, there was a bullous, confluent zoster eruption with intense erythema extending from the spinous processes of the second, third and fourth dorsal vertebras around the chest and axilla over the area between the second and fourth ribs to the sternum.

The patient was given 1 gm. of aureomycin by mouth 4 times a day, but she returned the next day complaining bitterly of pain and burning over the right deltoid area and in the axilla, which kept her awake throughout the night. A few new lesions had appeared along the posteromedial aspect of the right arm, over the triceps and down to the lower third of the forearm. The patient was reassured and was asked to continue taking the aureomycin, but no analgesic was prescribed. On the following day she returned, obviously happier, and stated that her pains had virtually stopped and that she had only slight burning over the vesicular area. The original lesions on the chest had now begun to dry. The patient had had one episode of vomiting 3 hours after one of the doses, so she was asked to take 0.5 gm. 4 times daily. On the 4th day there was minimal burning (chafing) in the axilla, and a few small dry crusts had already appeared. On the next day the dose was again dropped to 0.5 gm. 3 times a day because of nausea. By the 7th day the lesions had all dried up and were almost completely encrusted. There was one tender denuded area in the axilla but no evidence of secondary infection. The patient now complained of soreness of the tongue and mouth, but these areas looked normal. Aureomycin was stopped, and the soreness of the tongue and mouth subsided promptly. There was only slight residual burning over the axillary lesions and an occasional twinge of pain over the anterior portion of the chest in the next 2 days. Thereafter the patient was completely symptom free, and the lesions healed. There was no recurrence of the lesions and no post-herpetic pain.

TABLE 1. *Relevant Findings in 24 Cases of Herpes Zoster Treated with Aureomycin.*

CASE No.	SEX	AGE	HERPETIC LESION		AUREOMYCIN THERAPY			
			CUTANEOUS SEGMENTS*	STAGE	DATE BEGUN	DAYS AFTER ONSET	TOTAL DOSE†	
		yr.					*gm.*	*days*
1	M	72	T7-8	Late	Jan. 10	32	7.0+14.0	3+14
2	M	49	V_1+G	Initial	Jan. 25	4	12.0	3
3	F	65	V_1	Initial	Feb. 23	2	24.0	6
4	M	49	C3, 4	Late, acute	Feb. 25	10	12.0	5
5	M	52	T4-6	Late	Mar. 24	21	25.0	6
6	F	30	V_3	Acute	Apr. 1	4	12.5	4
7	M	25	L1-3	Acute	Apr. 21	7	12.5	4
8	M	60	T10-L1	Late, acute	May 5	14	9.0	3
9	M	65	T3, 4	Acute	May 19	7	12.0	3
10	M	80	V_1	Late, acute	June 3	13	37.5¶	9
11	F	61	V_3	Acute	June 13	3	17‖	9
12	F	74	T2-4	Late	June 13	17	15	6
13	F	79	$V_{1, 2}$	Acute	June 20	7	2‖	1
14††	M	72	V_1	Acute	July 8	3	31.0	9
15	M	78	T10-12+G	Acute	Aug. 3	7	19.0	7
16	M	65	C8, T1 & 4	Acute	Aug. 11	4	15.0	4
17	F	74	T4-6	Acute	Aug. 12	3	26.0	8+2
18	M	56	L2, 3	Acute	Aug. 18	7	20.0	6
19	F	72	T4, 5	Acute	Aug. 21	2	54.0	10
20	M	58	T7, 8+G	Late	Aug. 25	14	17.0	7
21	M	85	T4-6	Acute	Aug. 30	3	18.0	7
22	F	23	T1-4	Acute	Sept. 1**	8	7.5	5
23††	M	52	L3, 4	Initial	Sept. 8	3	22.0	6
24	F	58	T1-4	Acute	Sept. 8	6	16.5	7

*G = generalized eruption in addition to the segmental lesion, C = cervical, T = thoracic, and L = lumbar, the numbers indicating the segment; V_1, V_2 and V_3 indicate the cutaneous distribution of the ophthalmic, maxillary and mandibular branches, respectively, of the trigeminal nerve (V).

† + indicates 2 separate courses or 2 separate episodes.

‡Post-herpetic pain not prevented.

§Generalized lesions.

¶Patient also received aureomycin borate drops in the eye.

‖Two doses of 500 mg. given intravenously on successive days, in addition to oral doses.

**Patient relapsed promptly after cessation of treatment (initial response good).

††Negro patients.

ANALYSIS OF RESULTS

Some of the relevant data in the 24 cases are listed in Table 1. The total number of patients treated was not large, but an analysis of some of the major features will serve to bring out some of the points of interest in these results.

Effect of Sex and Age

There was a preponderance of males (15) over females (9). The patients ranged in age from twenty-three to eighty-five years, but, as usual in this disease, most of them were in the older age groups: only 5 patients were under fifty, 10 were fifty to sixty-nine and the remaining 9 were over seventy years old. There did not seem to be any correla-

tion between the sex or age of the patients and their response to aureomycin.

Effect of the Stage of the Disease When Aureomycin Was Started

Patients whose skin lesions were just beginning to appear when treatment was started are listed in Table 1 as treated in the "initial" stage; those whose erythematous lesions or clear vesicles were still appearing are listed as treated in the "acute" stage, and those treated after the middle of the second week, as judged from the onset of symptoms or the first appearance of skin lesions, are listed as "late" cases.

By these criteria, 3 patients were classified as being in the initial stage and aureomycin was started in them on the second to the fourth day; 14 others were considered to be in the acute stage and were first treated between the second to the seventh day. In all but 2 of these 17 patients the lesions and the symptoms began to show definite evidence of improvement after the first twenty-four hours of therapy. In some cases new lesions appeared during the first twenty-four to thirty-six hours but not later, except in 2 patients (Case 11 and 13), in whom oral therapy had to be interrupted. In both these cases the progress of the disease was then arrested, and marked improvement followed when aureomycin therapy was resumed and the antibiotic given for two days intravenously. The good effects were maintained in Case 11 by resumption of oral therapy, but in Case 13, in which no further therapy was given, there was another relapse. Post-herpetic pain was not prevented in either of these 2 patients. There was only 1 other patient in this group (Case 17) who had post-herpetic pain in spite of what seemed to be adequate treatment and a good immediate effect on both the lesions and the pain.

TABLE 1 (*Continued*).

CASE NO.	NO. OF DAYS AFTER START OF AUREOMYCIN†				ESTIMATE OF BENEFICIAL EFFECTS	DATE OF LAST FOLLOW-UP EXAMINATION
	NEW LESIONS APPEARED	LESIONS HEALED	PAIN STOPPED	ITCHING STOPPED		
1	18	32	>32	—	Probably none‡	Sept. 6
2	1§	7	2	2	Excellent	Sept. 16
3	0	5	2	5	Excellent	Sept. 20
4	0	3	—	3	Excellent	Sept. 30
5	0	6	?42	2	Good‡	Sept. 16
6	0	3	9	3	Excellent	Sept. 21
7	0	4	2	5	Excellent	Sept. 26
8	0	4	5	2	Good	Sept. 17
9	0	5	1	2	Excellent	Sept. 16
10	0	9–35	15	—	Moderate to good	Oct. 15
11	2	7	7+60	7	Good‡	Sept. 16
12	0	7	4+90	—	Good‡	Oct. 4
13	3–15	>90	3+90	3+9	Poor**	Sept. 26
14††	2	9	4	—	Good‡	Aug. 2
15	0	7	2	—	Excellent	Oct. 10
16	0	6	2	—	Excellent	Sept. 16
17	0	8	5+16	11+16	Good‡	Sept. 24
18	0	6	2	7	Excellent	Oct. 7
19	0	6	4	10	Excellent	Sept. 28
20	0	7	15	2	Slight	Sept. 20
21	0	8	4	8	Excellent	Sept. 26
22	1	6	5	—	Excellent	Oct. 2
23††	0	6	2	6	Excellent	Sept. 22
24	1	8	2	9	Excellent	Sept. 23

In 3 patients treatment was first undertaken on the tenth to the fourteenth day, but some of the lesions were fresh and new ones were appearing at the time. They are listed as "late acute." In 2 of these patients, Case 4 and 18, the response was similar to that of the early cases, whereas in the third (Case 10) the result may be considered as quite good in view of the severity of the lesion, the amount of secondary infection and damage present when aureomycin was started and the usually poor prognosis in such cases.

Four patients were treated late in their diseases. In 3, aureomycin was started between the fourteenth and twenty-first days, and their lesions and pain improved promptly; in the fourth, treatment was

started with small doses during the fifth week and there was essentially no effect. Post-herpetic pain occurred in 3 of these 4 patients; the only one among them who did not have a recurrence or persistence of pain was the one whose treatment was started on the fourteenth day.

It therefore seems that the best results were obtained in the patients who were treated on or before the middle of the second week after the first appearance of symptoms or lesions. New lesions did not appear after the first day of therapy, and then the pain subsided, the lesions dried up, and healing progressed rapidly. When treatment was interrupted early, new lesions soon appeared and pain recurred, and the progress of the lesions was again arrested by resumption of therapy. In an occasional case, post-herpetic pain appeared in spite of early and adequate treatment. In the patients treated after the end of the second week, there may have been some beneficial effect on the lesions, and there was immediate alleviation of the pain, but the post-herpetic pain was not prevented.

Effect on the Lesions

Rapid evolution and clearing of the lesions usually began within or shortly after the first twenty-four hours of aureomycin therapy. The intense erythema, when present, lessened quite promptly. The vesicles then began to dry and were usually well dried up and encrusted between two and four days after the first dose. Complete healing occurred in the great majority of cases by the seventh or eighth day, when there was left either no trace of the lesions or only a faintly erythematous scar at the site.

Appearance of New Lesions

There were 3 patients (Case 2, 22 and 24) in whom new lesions continued to appear during the first day of therapy and a fourth (Case 14) in whom such lesions occurred during the first two days while full doses of aureomycin were given. In Case 2 these were generalized lesions. In these 4 patients all the lesions began to dry up shortly thereafter, and the progress of the disease was otherwise favorable. In 3 other patients (Case 1, 11 and 13) new lesions appeared only after the early interruption of therapy.

Effect of the Site of the Lesion

There were 5 patients in this series in whom the lesions involved the cutaneous distribution of the ophthalmic branch of the trigeminal nerve, and in 1 of them the area of distribution of the maxillary nerve was also affected. One of these patients (Case 10) already had severe secondary infection of the conjunctivas with a mixture of pyogenic organisms, and there was also involvement of the cornea with herpetic lesions. In addition, this patient had marked nitrogen retention. The progress of the herpes was promptly arrested after aureomycin was started, and the secondary infection cleared but recurred shortly after the therapy was stopped. Another of these patients (Case 13) was the one who would not continue treatment, and the lesions progressed after temporary improvement; this patient was the only one in whom there was a residuum of corneal damage and impairment of vision. The 3 remaining patients with ophthalmic herpes zoster all responded favorably and did not have any corneal lesions.

There was also 1 patient with involvement of the area of the mandibular branch and another in whom the herpes involved the maxillary branch of the trigeminal nerve. In both these patients treatment was begun early. The lesions in the former cleared rapidly; the latter (Case 11) was the one whose lesion progressed when treatment was interrupted but again improved when aureomycin was resumed.

The remaining patients all had involvement of the trunk and extremities.

Generalized Herpes Zoster

In addition to the segmental lesions there were 3 patients (Case 2, 15 and 20) who had isolated lesions or small groups of vesicles over all other parts of the body. In 2 patients they were present at the time aureomycin was started, and in the third they appeared during the first few hours after the first dose was given. These lesions all cleared promptly and completely after the aureomycin was started.

There was no clinical evidence of central-nervous-system involvement in any of these or any of the other patients in this series. Lumbar punctures, however, were not done to determine whether there was any asymptomatic involvement.

Effect on Pain

The immediate effect on the pain was quite striking. Severe pain and itching were markedly reduced after the first twenty-four hours of therapy and were usually completely relieved in four or five days. In a few patients, however, the pain continued with diminishing intensity for a few days longer.

Post-herpetic pain was mentioned above. This late pain was not prevented in 6 of the patients, including 3 in whom therapy was started after the middle of the third week of the disease and a fourth (Case 13) in whom therapy was interrupted and not resumed. In the other 2 patients the post-herpetic pain occurred in spite of early and seemingly adequate therapy and in spite of a good response of the skin lesions. In 1 of the latter (Case 17) an attempt was made to influence the pain by further aureomycin therapy. This was given for only two days, and the patient stated that the

pain decreased slightly in intensity but the benefit derived was not considered sufficient to warrant continuing the therapy.

Dosage

The total dose used in these cases (excluding Case 13) varied from 7.5 to 54 gm. and was given over periods ranging from three to seventeen days. Three fourths of the patients were treated for three to seven days, and all but 4 received 25 gm. or less. The average was about 19 gm. given in six and a half days. From these observations, the dose recommended at present is 4 gm. daily until the lesions show definite signs of healing — usually about two to four days — and 2 gm. daily for three to five days longer. The daily dose may be divided and given after each meal and on retiring.

Untoward Effects

The only evidence of any toxic effects from aureomycin was the occurrence of nausea in most of the patients. There was occasional vomiting in some, and a few had large, bulky bowel movements. These manifestations were usually encountered only during administration of the full doses of 4 gm. or more daily, and nausea or vomiting was particularly apt to occur when individual doses of 1 gm. each were taken on an empty stomach. They usually did not appear until after the second or third day and at a time when the lesions already showed signs of regressing. They were readily controlled in most of the patients by reduction of the dose, and only rarely were they severe enough to interfere with effective therapy. In such cases the drug could be given intravenously without untoward effects. There was 1 patient in whom angioneurotic edema of the tongue and mild generalized urticaria occurred after six days of oral administration of aureomycin, but this patient also received other drugs (codeine and barbiturates), which might have been responsible for these manifestations, and the toxic effects cleared promptly after all medications were stopped.

Follow-up Study

Some of the patients were seen frequently after their aureomycin therapy was ended, and all but 1 were seen or heard from shortly before this report was completed. The last observation in these cases was made from six to eight months after therapy was started in 6 patients, after three to six months in 7, between five and ten weeks in 5 and after two to four weeks in the remaining 6 patients.

The occurrence of post-herpetic pain in 6 patients was mentioned above; this lasted from two weeks up to three months.

In only 2 patients was there a recurrence and extension of the skin lesions after therapy was stopped. One of these was the first patient treated, and the aureomycin was started during the fifth week and only small doses were used; the other was the patient (Case 13) who refused further treatment after two intravenous doses and relapsed after leaving the hospital. This was the only patient who had residual corneal opacities and impairment of vision.

In most of the patients in whom treatment was started early the site of the original lesions was no longer discernible. In a few there were some superficial scars, and in others there was slight pigmentation in some of the sites of the lesions.

Discussion

The cases presented above strongly suggest that aureomycin has a definite, beneficial effect on the course of herpes zoster. It should be emphasized, however, that although these results were obtained in consecutive cases, no parallel control series of cases was observed either without therapy or under other forms of therapy. The feature of these results that suggests a highly beneficial, if not a specific, effect is the fairly regular and characteristic response in all patients receiving adequate amounts of this antibiotic in the early or active stage of the disease.

It seems highly unlikely that this benefit is wholly the result of an effect on secondary bacterial infection. Although such an effect undoubtedly played a part in some of the cases, there was no evidence of bacterial infections in most of the patients. Furthermore, other potent antibacterial agents, notably penicillin, have not had any similar effect although they may have favorably influenced the pyogenic component of the lesions. Perhaps more significant is the fact that new herpes-zoster lesions have not developed during aureomycin therapy except during the first day or so, although such lesions have appeared after treatment was interrupted too soon.

Mention has been made by one reliable observer[36] that herpes zoster has developed during the course of aureomycin treatment for other infections that occurred after nephrectomy. In a personal communication Schoenbach has mentioned another patient who was treated for a urinary-tract infection following a left nephrectomy and in whom "herpes zoster" developed on the right lower quadrant and back on the seventh day of aureomycin treatment (2 gm. daily) and 2 weeks after the nephrectomy. In view of these cases, the estimate of the specific value of aureomycin in this disease, as suggested by the experience in the present series of cases, may have to be revised.*

Results similar to those noted in these cases have been reported from Chloromycetin in 4 cases that were treated in the acute stage. Post-herpetic pain

*Schoenbach, in a personal communication, has also observed 3 patients with typical herpes zoster who showed a rapid clinical improvement similar to those described in this paper. These 3 patients had not had any operations.

was not affected by the Chloromycetin in 2 other cases.[32] Initial experiences in 3 early cases of herpes zoster treated with Chloromycetin in this clinic seem to substantiate these findings.

It is to be borne in mind that many other agents have, in the past, been claimed to have striking and specific effects in this disease.[37] These will not be reviewed here. Suffice it to say that none of them have thus far gained acceptance or wide use as specific therapeutic agents for herpes zoster. Further experience will be necessary to ascertain the true value and place of aureomycin (and Chloromycetin).

Brief mention may also be made of aureomycin in herpes simplex. Claims have been made of beneficial effects from this antibiotic in patients with skin lesions considered to be due to the virus of herpes simplex[29-31] (herpes labialis and Kaposi's varicelliform eruption). We have observed several cases in which the lesions of herpes labialis healed fairly rapidly under systemic treatment with aureomycin. Some of these patients believed that they were definitely benefited by the aureomycin in that their lesions healed much more rapidly than they had in previous similar episodes. Most of these patients, however, had coincident impetiginous lesions or superimposed staphylococcal and streptococcal infections, and the improvement could be interpreted as a result of the effect on these secondary infections.

As opposed to these apparently favorable results, at least 4 patients have now been observed in this hospital in whom characteristic herpes labialis appeared and extended during treatment with full doses of aureomycin given for acute bacterial infections.[38] The latter observations are much more significant and render it unlikely that aureomycin has a specific action against herpes-simplex infections. It is possible, of course, that multiple agents are involved in the etiology of these types of lesions or that there are strain differences in the susceptibility of the herpes virus to aureomycin. This possibility must also be considered, of course, in cases of herpes zoster.

Summary

The relevant findings in 24 cases of herpes zoster treated with aureomycin are presented.

Aureomycin appeared to halt the progress of this disease and to bring about rapid healing of the lesions. Vesicles dried up and became encrusted in the first two to four days after treatment was started and proceeded to heal rapidly and completely thereafter. In occasional patients new lesions appeared during the first day of treatment but not later unless the therapy was interrupted.

The pain accompanying the acute lesions also subsided after the first day of therapy. Post-herpetic pain rarely occurred in the patients whose treatment was begun early and was maintained in adequate dosage, but it was not prevented in the patients in whom treatment was begun more than two weeks after the first appearance of the lesions.

The oral dosage found to be effective in these cases was 4 gm. daily (1 gm. after each meal and at bedtime) for two to four days, or until the lesions were well dried and encrusted. Half this dose is given for an additional three to five days and may also be used throughout when the larger doses are not tolerated. Intravenous doses of 500 mg. daily likewise appear to be effective and may be used if the oral dose is not well tolerated. The optimum intravenous dosage, however, was not ascertained.

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PROTHESIS FOLLOWING HEMIPELVECTOMY*

JOHN F. COOPER, M.D.,† AND GRANTLEY W. TAYLOR, M.D.‡

WEST ROXBURY, MASSACHUSETTS

A MAJOR problem in the rehabilitation of patients subjected to hemipelvectomy has been the adaptation of a suitable prosthetic appliance. Owing to the rarity of this type of amputation, both the surgeon and the artificial-limb manufacturer have had few opportunities to clarify the problem. The purpose of this report is to present an efficient prosthetic appliance of this character and to record a case of its successful use.

In the last half century 138 cases of hind-quarter amputation have been reported in the literature. This radical surgical procedure was first performed successfully in 1895 by Girard[1] and later standardized by the methodical work of Hogarth Pringle[2] in 1916. Later reviews of the subject with presentation of cases were recorded by Judin,[3] Gordon-Taylor,[4, 5] Leighton,[6] Morton,[7] Sugarbaker[8] and Pack et al.[9, 10] The last authors, in their comprehensive work on exarticulation of the extremities for cancer, reaffirm the idea that a useful prosthesis has never been devised for these patients subjected to hemipelvectomy. Perforce, the patient learns to sit on the remaining ischial tuberosity and becomes adept in the use of crutches.

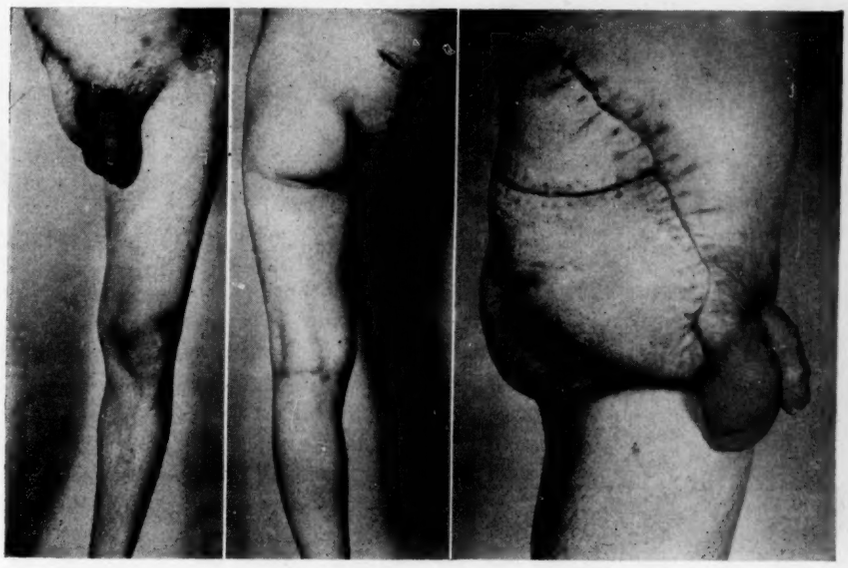

FIGURE 1. *Extent of Amputation.*

It is recognized that the successful adaptation of a prosthesis in these cases is difficult and wholly dependent upon the personality and physical status of the patient. A lithe, young, energetic and cooperative patient naturally possesses greater potentialities for complete rehabilitation than the apathetic, more passive subject. The case reported below represents the successful prosthetic reha-

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†Assistant resident in surgery, Veterans Administration Hospital.

‡Consultant in surgery, Veterans Administration Hospital.

bilitation of an agile and earnest young man who made a rapid recovery after hemipelvectomy for a chondrosarcoma of the acetabulum.

Case Report

F. R., a 24-year-old Navy veteran, was admitted to the Orthopedic Service of the Veterans Administration Hospital, West Roxbury, Massachusetts, on April 21, 1947, complaining of recurrent pain in the right hip of 4 years' duration following minor trauma. This pain had a tendency to develop while the patient was at rest, particularly in the sitting position.

The past and family histories were noncontributory.

Physical examination was entirely negative except for limited motion of the right hip. X-ray study revealed a destructive cystic process involving the right acetabulum. Pertinent laboratory studies revealed only an elevated blood cholesterol of 240, 275 and 289 mg. per 100 cc., and an alkaline phosphatase of 5.3 Bodansky units. X-ray films of the chest and a bone series were normal.

Biopsy of the lesion on May 5, 1947, demonstrated numerous, free, cartilaginous bodies within the joint space. A pathological diagnosis of chondrosarcoma was made on

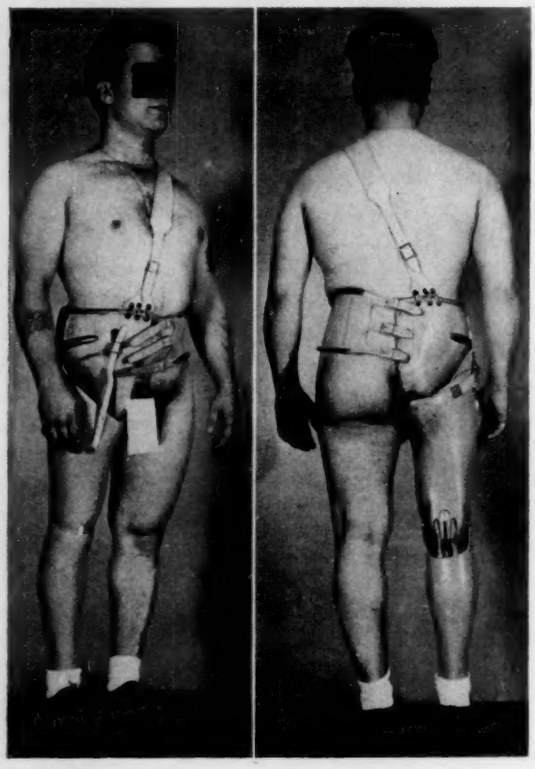

Figure 2. *Patient with Prosthesis in Place.*

examination of this material. At a later date a right sacroiliac disarticulation was performed, and the patient made a remarkably rapid and uneventful recovery. He was soon able to be about on crutches with surprising agility. Pathological examination confirmed the original diagnosis and disclosed disease arising in the acetabulum with invasion of the ilium to within 1 or 2 mm. of the pelvic surface. There was also moderate involvement of the femoral neck and joint capsule. Repeated follow-up x-ray examinations of the chest have been negative for metastasis.

Discussion

The prosthetic appliance was not provided for the patient until six months had elapsed. During that time adequate shrinkage of the stump had occurred and sufficient consolidation of tissue had taken place so that weight bearing was possible. It should be realized that no true stump was actually present but only a soft-tissue mass composed of anterior and posterior abdominal parietes, which provided weight-bearing surface.

The prosthesis itself was of the conventional willow-wood type with the usual knee and ankle articulation designed in the standard fashion of all artificial-limb manufacturers. In addition to

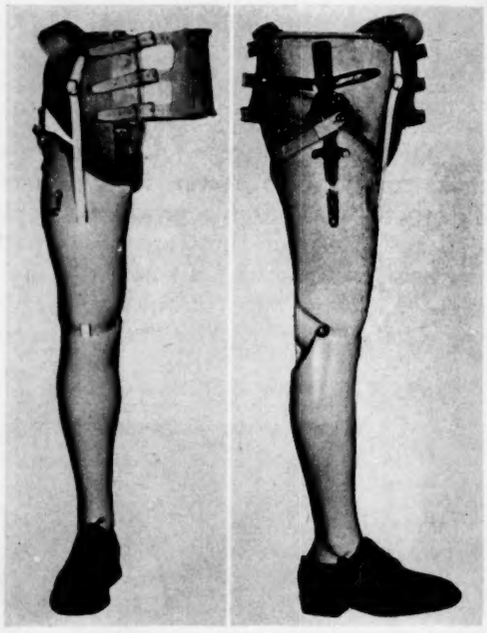

Figure 3. *Photograph of the Prosthetic Appliance.*

these articulations, a steel hip-joint device, which locked in extension and could be readily released for flexion of thigh in the sitting position, was developed. A preliminary cast of the amputation site enabled the manufacturer to evolve a "leather bucket" composed of molded laminated cowhide, which closely approximated the contours of the stump. This was fashioned so that weight was borne on the soft-tissue mass anteriorly, laterally and inferiorly, without direct pressure on the coccyx or opposite ischial tuberosity. To ensure union of the prosthesis and patient there was a wide abdominal belt fastening anteriorly, with the added support of a broad shoulder strap applied over the left shoulder.

The problem of stability of the patient in motion was solved in an ingenious manner by the limb maker. It was recognized that the sound limb of the subject was the keystone of stability and function, and therefore the artificial limb was so designed as to compel the subject to utilize it as a secondary aid in locomotion rather than a primary one. Thus,

it was found necessary to displace the center of gravity of the artificial limb several inches laterally to force the patient to shift his weight to his sound limb after initially bearing weight on his prosthesis. In this manner any tendency to shift weight toward the prosthetic or unstable side of the body in motion was effectively minimized.

With the foregoing type of prosthesis the patient rapidly became ambulant and manifested complete satisfaction with his appliance. The extent of the amputation, the patient with the prosthesis applied and the applicance itself are shown in Figure 1 to 3. At present he is able to walk without the aid of a cane or crutch, with only a moderate limp resulting from the required shortening of the appliance. He is able to ascend and descend several flights of stairs with ease. The only apparent disadvantage is that he requires considerable aid in attaching his prosthesis, which is bulky and difficult for him to apply without assistance.

Summary

Adaptation of a prosthetic appliance after hemipelvectomy has proved a difficult problem in the past. This is apparent in a review of the current literature. A case of chondrosarcoma of the acetabulum in which the patient was subjected to hemipelvectomy, with subsequent complete rehabilitation as a result of the development of a suitable and efficient artificial limb, is presented.

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MANAGEMENT OF TRIAL LABOR*

Thomas F. Foley, M.D.†

MANCHESTER, NEW HAMPSHIRE

OBSTETRIC patients usually fall into three broad clinical groups. First, a fairly large number have normal pelvic measurements and satisfactory labor and deliver without difficulty. Secondly, a very small number have pelvic measurements that make normal delivery impossible, with cephalopelvic disproportion evident both clinically and by x-ray examination — it is readily apparent that elective cesarean section is indicated for these patients. Thirdly, a large number have what might be termed "border-line" pelvic measurements that place them in the mind of the examiner as suspects for cephalopelvic disproportion. The prognosis for delivery through the pelvis in the third group may be somewhat doubtful. It is this particular group that I should like to discuss, because conservative management will result in a high percentage of uncomplicated pelvic deliveries if the patients are given a trial labor.

It may be well to recall that there are five components of cephalopelvic disproportion: the size and shape of the pelvis; the size of the fetal head; the position and presentation of the fetus; the degree of molding to which the head is subjected; and the force of the labor pains. Of these, only the first, the size and shape of the pelvis, is susceptible to accurate measurement before labor begins. Current methods of fetal cephalometry have not proved satisfactory.

The final position and presentation cannot be adequately determined until the onset of labor, because an unfavorable presentation is often converted into a more favorable one by the forces of labor. The most important factor in determining the outcome in the group under discussion is the *quality* of the labor pains. One has no way of predetermining the nature of the labor. The quality of the labor pains is important, because satisfactory labor will frequently more than compensate for small pelvic diameters, and a normal pelvic delivery will result.

I do not wish to place too much emphasis on x-ray pelvimetry, but when the question of cephalopelvic disproportion arises it is very helpful toward intelligent management of the situation. X-ray examination of the pelvis is indicated if the clinical examination discloses such unfavorable signs as the ability to touch the promontory easily on vaginal examination, angulation of the sacrum, narrowing of the outlet and failure of a primipara to engage at term, to mention only a few.

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†Associate obstetrician, Elliot Hospital.

The management of a trial labor is essentially the management of *any* labor in addition to the adherence to certain definite principles from the outset. It is important in the conduct of a trial labor to set some reasonable time limit on the length of the trial period. I believe it is fair to state that if after twelve to fifteen hours no progress has been made, the termination of labor by abdominal delivery should be considered. Many factors enter into an evaluation of whether the patient has or has not made progress. Three significant signs or symptoms indicating progress are — effacement and dilatation of the cervix, increase in the strength and frequency of the labor pains and descent of the head. The last is positive evidence that the patient has made progress.

Lateral films taken at intervals during labor offer concrete proof of whether or not the head was descended. Progress or the lack of progress is the decision that the obstetrician must make as the end of the trial period approaches.

I should like to offer a word of caution regarding strict asepsis during labor. It should be constantly remembered throughout a trial labor that the patient is a potential candidate for cesarean section, and therefore, all examinations should be conducted aseptically. The number of rectal examinations should be reduced to an absolute minimum and not more than one sterile vaginal examination should be permitted during a trial labor.

MEDICAL PROGRESS

VITAMIN SUPPLEMENTATION IN HEALTH AND DISEASE (Concluded)*

PERRY J. CULVER, M.D.†

BOSTON

NEWER VITAMINS

During the last four years, an important place in medical literature has been given to the discovery and therapeutic uses of three newer vitamins that promise much for man. These three substances are folic acid, vitamin B_{12} and rutin or vitamin P. At present it is impossible to ascertain whether the clinical response to these supplements is due to alleviation of a deficiency of the specific newer factor or whether benefit results from a pharmacologic effect.

Folic Acid

The fast-moving history of the discovery, identification, synthesis, physiology and therapeutic uses of folic acid was well reviewed by Sargent[8] in 1947. To paraphrase his summary, folic acid is known chemically as pteroylglutamic acid, which is the active form of this newer member of the vitamin B complex. The vitamin occurs in many foods such as liver, green vegetables, kidneys and yeast, but it is usually in the physiologically inactive conjugated form, pteroylheptaglutamic acid (vitamin B_c conjugate). An enzyme, vitamin B_c conjugase, which liberates the active pteroylglutamic acid, is present in many mammalian tissues. Foods contain a conjugase inhibitor, which impedes the hydrolytic activity of the vitamin B_c conjugase. The amount of pteroylglutamic acid in the ordinary diet is far less than the usual therapeutic level of folic acid, which is estimated at 5 to 10 mg. daily.

Pteroylglutamic acid has been effective in promoting a hematopoietic response in the various macrocytic anemias, in some of the sprue syndromes and in certain cases of "chronic diarrhea" due to nutritive failure. The natural heptapeptide, pteroylheptaglutamic acid, was found to be ineffective in Addisonian pernicious anemia, whereas the synthetic pteroylglutamic acid was utilized. The explanation of this observation is that patients with Addisonian pernicious anemia are unable to neutralize the conjugase inhibitor. Initial enthusiasm for the use of folic acid in Addisonian pernicious anemia was soon dampened by reports of the explosive appearance of neurologic complications in such cases, and for this reason the management of Addisonian pernicious anemia with pteroylglutamic acid was not recommended.

Folic acid was found to have no effect on the anemias associated with iron deficiency, cancer, leukemia and lymphoma, nor on aplastic anemia, agranulocytosis and thrombocytopenic purpura.

The numerous reports on folic acid that have appeared since Sargent's review primarily confirm the findings already summarized, but some clarify certain doubtful points and more definitely define the final place of folic acid in therapeutics.

There has been considerable discussion of the relative hematopoietic effect of folic acid as compared with liver extract. Frommeyer and Spies[171]

*From the Medical Clinics, Massachusetts General Hospital, and the Department of Medicine, Harvard Medical School.

†Associate in medicine, Harvard Medical School; assistant in medicine, Massachusetts General Hospital.

observed that the hematologic response to folic acid paralleled that which followed treatment with concentrated liver extract in cases of macrocytic anemia, but the rate of regeneration was greater with a potent liver extract. Berk et al.[172] reported the reticulocyte responses and initial rises in the red-cell count and hemoglobin of 12 patients with pernicious anemia treated with daily doses of 10 mg. of folic acid intramuscularly to be comparable to those seen with purified liver extract. In general, the evidence is against folic acid in cases of Addisonian pernicious anemia and nontropical sprue. Hall and Watkins[173] found that the maximal reticulocyte response was lower after folic acid therapy as compared with liver extract, and that in 3 cases the red-cell count did not increase above 3,500,000 despite prolonged treatment with folic acid. An unsatisfactory hematologic response to folic acid was observed in 9 of 10 patients with the sprue syndrome, but these patients had a normoblastic bone marrow, although their peripheral red blood cells were macrocytic.[174] A similar observation was made by Weir and Comfort.[175] There are even reports of hematologic relapses in Addisonian pernicious anemia during prolonged therapy with adequate doses of folic acid[176-178] but with subsequent remissions after administration of liver extract. Jones et al.[179] also record a case of nontropical sprue in which a hematologic relapse developed after good initial response to folic acid and the patient subsequently improved with vitamin B_{12} therapy.

In contrast to these two diseases, folic acid has proved to be effective hematopoietically in other types of megaloblastic anemia that are refractory to liver extract and vitamin B_{12}.[180-183]

The failure of folic acid to alleviate or prevent the neurologic sequelae of Addisonian pernicious anemia has been reported by so many investigators that nearly all clinicians agree with the advice of an editorial in the *Lancet*,[184] which states, "The practical lesson is clear and agreed: folic acid whether alone or with liver extract must not be given to patients with pernicious anaemia." The chief controversy over the use of folic acid concerns its possible toxic effect on the central nervous system. Neurologic manifestations of pernicious anemia appear with much greater frequency after treatment with folic acid than in untreated cases.[185] This complication after folic acid therapy is also more precipitous in nature and involves the posterior columns of the spinal cord more completely than the lateral columns.[186] Such observations suggest that the resultant effect of folic acid on the central nervous system is not identical with "combined-system disease."

Neurologic complications of folic acid therapy are not limited to Addisonian pernicious anemia alone. An occasional case of peripheral neuritis after folic acid therapy for other macrocytic anemias has been reported.[187, 188]

Some investigators have believed that folic acid was actually toxic to the central nervous system.[189] This seems to be a minority view, because of the small number of cases other than Addisonian pernicious anemia that have had neurologic complications after prolonged folic acid therapy.[189, 190] The occasional case of glossitis or other characteristic signs of vitamin deficiency that appear during the prolonged administration of folic acid is explained on the basis of vitamin imbalance. In view of these observations, it is probable that the peripheral neuritis and possibly the central-nervous-system symptoms associated with folic acid therapy actually represent another manifestation of vitamin imbalance rather than true toxicity.[188]

The mechanism whereby folic acid produces a hematologic response is not known. In fact, there is no evidence that there is a dietary deficiency of folic acid in these diseases, but perhaps an impairment in the utilization of folic acid. On the other hand, in the nutritional deficiency disease, tropical sprue, the remarkable effectiveness of folic acid, which has been so well established by Suarez et al.,[191] seems to indicate that tropical sprue represents a true primary folic acid deficiency. The effect of folic acid in nontropical sprue has been clinically beneficial according to some observers.[174, 192] Darby and his associates[192] noted the return of glucose tolerance tests toward normal in 5 out of 6 cases of nontropical sprue after folic acid therapy, and improvement in the vitamin A absorption curve in 2 cases. Other investigators have not observed any striking benefit of folic acid in cases of nontropical sprue.[175, 193] This difference in result may be due to the fact that cases of idiopathic steatorrhea that do not respond to folic acid are not nontropical sprue but represent fatty diarrhea from other causes.[192] It is possible, however, that some cases of nontropical sprue do not respond to folic acid because the disease has reached an irreversible stage. The mode of action of folic acid in nontropical sprue is not replacement therapy for a deficiency state, since most of these patients have had an adequate diet; however, the therapeutic effect of folic acid may represent a pharmacologic manifestation.

As a result of the investigations that have appeared since Sargent's[8] review, the place of folic acid in nutrition is now more clearly defined. The vitamin is effective in certain liver-refractory macrocytic anemias and is almost specific for the malnutrition state of tropical sprue. The neurologic complications, glossitis and pellagra associated with folic acid therapy seem to be best explained by vitamin imbalance rather than the toxic effects of folic acid. This member of the vitamin B complex does not have the same hematopoietic effect as liver in the treatment of Addisonian pernicious

anemia, and the necessity for using folic acid in cases of pernicious anemia that are sensitive to liver extract no longer needs to be considered, since the discovery of vitamin B_{12}.

Vitamin B_{12}

After one false stop at folic acid, the twenty-year search for the antipernicious-anemia factor of liver extract appears to have achieved its goal with the discovery of vitamin B_{12}. In 1948 Rickes et al.[194] reported the isolation from concentrated liver extracts of minute quantities of a red crystalline material, which Shorb[195] found to be eleven thousand times more active than potent liver extracts by a bioassay method that appeared to be very specific for the antipernicious-anemia factor. The clinical effectiveness of this crystalline material was demonstrated by West,[50] who found that 3, 6 and 150 gamma of vitamin B_{12} produced a positive hematologic response in 3 cases of Addisonian pernicious anemia. The crystals were named vitamin B_{12} because that term was nonspecific and connoted only nutritional significance.[194] Although the chemical nature of vitamin B_{12} is still undetermined, further investigation has shown it to be a cobalt complex.[196] This is the first time that cobalt has been shown to be an essential trace element in human nutrition. The red color of the crystals is explained in part at least by their cobalt content. The vitamin is heat stable but is inactivated at room temperature in dilute alkaline or dilute acid solutions.[196]

Scarcity of vitamin B_{12} greatly limited its clinical trial at first. The presence of vitamin B_{12} activity in many foods led to the search for a more plentiful source of this factor, and *Actinomyces* (*Streptomyces*) *griseus* was found to produce a red crystalline substance that had the same physical, biologic and clinical properties as vitamin B_{12} from liver.[197, 198] As a result, crystalline vitamin B_{12} from *A. griseus* is now readily available and relatively inexpensive.

A rapidly growing number of reports confirm West's original observation of the hematologic effectiveness of intramuscular vitamin B_{12} in patients with pernicious anemia,[179, 199-202] and the vitamin produces responses equal to those obtained with liver extract in cases of nutritional macrocytic anemia,[179, 199, 203] nontropical sprue[179, 199] and tropical sprue.[203] Adequate doses of vitamin B_{12} produce a maximal reticulocyte response in four to nine days[200, 203] and restoration of the red-cell count, white-cell count and platelets to a normal level in four to eight weeks, but in some cases, Hall and Campbell[200] observed that after 8 weeks of therapy with as much as 160 gamma of vitamin B_{12}, the red-cell count reached a plateau at 4,000,000 to 4,500,000. This incomplete response was attributed to either inadequate dosage or the elderly state of the patients. The rapidity with which the bone marrow changes from a megaloblastic to a normoblastic state is amazing. Within nine hours of the injection of 1 gamma of vitamin B_{12}, definite maturation of the megaloblasts was noted,[200] and complete restoration of the bone marrow to a normal state occurred within forty-eight to ninety-six hours.[200, 202] Clinical improvement in cases of pernicious anemia occurred within two to five days of the onset of therapy.[202, 203] Patients with tropical sprue showed a decrease in bowel movements and abdominal distention six or seven days after treatment was begun.[203]

The inadequacy of folic acid in preventing the development of central-nervous-system complications in patients with Addisonian pernicious anemia led to the postulation of a deficiency of two liver factors in pernicious anemia. One factor was folic acid, which promoted the maturation of erythrocytes, and the other a hypothetical nutrient required for the prevention of neurologic damage. Such a postulation became unnecessary when Berk et al.[204] found that vitamin B_{12} caused a marked improvement in the neurologic symptoms that developed in a patient with pernicious anemia who was receiving pteroylglutamic acid. As a result of this observation, later confirmed by others,[201-203, 205] Berk and his co-workers[206] stated that a deficiency of vitamin B_{12} may be closely related to the natural origin of both the blood and nervous changes of pernicious anemia. The glossitis of pernicious anemia also responds to vitamin B_{12},[201, 202, 205] a fact that adds weight to the belief that vitamin B_{12} is the antipernicious-anemia factor of liver extract.

A new concept of the pathogenesis of pernicious anemia and of the role of the intrinsic factor has resulted from experiments with oral administration of vitamin B_{12} to patients with Addisonian pernicious anemia. Berk et al.[206] found that oral administration of vitamin B_{12} was ineffective hematopoietically, but when given orally with neutralized gastric juice from a normal person, vitamin B_{12} elicited a reticulocyte response of as much as 16 per cent with a rise in the red-cell count. A similar observation is reported by Spies and his associates.[203] Fecal analysis for vitamin B_{12} activity[201, 206] showed an excretion of many times the amount of vitamin B_{12} needed for treatment. These findings suggest that vitamin B_{12} is closely related to the extrinsic (food) factor and that the purpose of the intrinsic (stomach) factor is to promote absorption of vitamin B_{12} from the intestinal tract, rather than to react with the extrinsic factor to produce the erythrocyte maturation factor. Consequently, the fundamental defect in Addisonian pernicious anemia may be inadequate intestinal absorption due to a deficiency of intrinsic factor.

Another property of vitamin B_{12}, unrelated to the macrocytic anemias, is an unconfirmed report

of its diuretic action in 12 of 16 patients with normal blood pictures.[207] The investigators who report this finding speculate that large doses of vitamin B_{12} may cause a vasodilation owing to the action of cobalt.

The minimal and optimal dosage of vitamin B_{12} has already become the subject of considerable difference of opinion. On the basis of the original reports, it was believed that 1 gamma of vitamin B_{12} was approximately equal to 1 *U. S. P.* unit of liver extract,[194] and bioassay of several commercial liver extracts showed that vitamin B_{12} might have an even greater potency.[194] Subsequent clinical trials showed that 1 gamma of vitamin B_{12} per day produced a maximum reticulocyte response in some cases [200, 201] and that, by comparison of the rates of increase in red-cell count, 1 gamma of vitamin B_{12} was approximately equal to 1 *U. S. P.* unit of liver extract.[198]

Sturgis[208] reports that as little as 0.45 gamma of vitamin B_{12} per day will produce a definite although substandard hematologic response. The general consensus is that the rate of utilization of vitamin B_{12} approximates 1 gamma per day and with daily administration at this level, there is no storage of the vitamin.[179]

Some investigators believe that the reticulocyte response does not parallel the rate of hemoregeneration and that the latter is a truer measure of vitamin B_{12} activity.[179, 209] By such determinations it is shown that more than 1 gamma of vitamin B_{12} per day is necessary for a maximum rate of erythropoiesis,[179] and Jacobson[209] believes that 3 or 4 gamma per day is needed to achieve the maximum rate of red-cell regeneration.

Jacobson[209] also suggests that 3 or 4 gamma of vitamin B_{12} may be needed to equal the biologic activity of 1 *U. S. P.* unit of liver. He explains this observation, which is at variance with the bioassay measurement of vitamin B_{12} in terms of *U. S. P.* liver units,[194] by postulating the presence of accessory factors in liver extract that may be important for the therapeutic activity of vitamin B_{12}.[209]

The controversy about the *U. S. P.* liver-unit value of 1 gamma of vitamin B_{12} appears to be merely one of definition — namely, the measure of 1 *U. S. P.* unit of liver. Since crystalline vitamin B_{12} is administered in weighed amounts, it can be expected to produce more uniform clinical results than liver extract, whose potency may be rather variable because it is established by bioassay. Moreover, the differences of opinion about the values for the minimal and optimal doses of vitamin B_{12} could be explained easily on the basis of the differences in requirement among the various patients with pernicious anemia. A safe working rule might be to administer 15 to 25 gamma of vitamin B_{12} per week until the red-cell count had returned to normal and then to maintain the patient on a dose approximating 1 gamma per day.

Vitamin B_{12} has other advantages over liver extract in that the vitamin, which seems to be nonallergenic, can be safely administered to patients who are sensitive to liver extract,[204] and much larger amounts of the antipernicious-anemia factor can be given in a single dose of vitamin B_{12}.

The specificity of pteroylglutamic acid for certain anemias and of vitamin B_{12} for others offers promise of a better understanding of the nature of the macrocytic anemias.

Rutin (Vitamin P)

Vitamin P, first described in 1936 as a possible food factor associated with the integrity of the walls of blood capillaries,[210] did not get an adequate clinical trial until 1944, when Griffith et al.[211] reported that rutin had restored the increased capillary fragility to a normal state in 8 of 11 cases associated with hypertension.

The term vitamin P encompasses several closely related flavone glucosides derived from plants. Various forms of the vitamin have been known as citrin, hesperidin and rutin.[212] Citrin is a crude product containing vitamin C as well as hesperidin and other flavone glucosides. Hesperidin and rutin are pure crystalline products. The clinical response to vitamin P has been determined by changes in the capillary-fragility test[211, 212] and by clinical improvement. The specificity of vitamin P for the treatment of increased capillary-fragility states seems well established by the recurrence of increased capillary fragility when vitamin P therapy is discontinued and subsequent restoration of normal fragility with readministration of the vitamin.[211] On the basis of a small number of observations, Shanno[212] expressed the belief that rutin might be superior to hesperidin.

The spectrum of therapeutic indications for vitamin P continues to broaden as an increasing number of clinical observations are published. Shanno[212] found that rutin was of value in preventing vascular accidents in patients with hypertension, maintaining normal capillary fragility in patients being treated with thiocyanate and controlling pulmonary bleeding of an unexplained nature but associated with increased capillary fragility. Rutin offers hope of being a specific remedy for the treatment of familial hemorrhagic telangiectasia.[213]

The capillary fragility was improved by doses of vitamin P ranging up to as much as 300 mg. per day in two series of diabetic patients who showed diabetic retinopathy, but in neither series was there any evidence that vitamin P improved the pathologic state of the eyegrounds.[214, 215] On the other hand, MacLean and Brambel[216] observed 21 patients with vascular retinopathies, other than diabetic, in which rutin and Dicumarol together

resulted in sufficient improvement to warrant further trial with this type of therapy. Twenty patients with long-standing arthritis who were shown to have increased capillary fragility were studied by Warter et al.[217] The patients were divided into three groups, one receiving 200 mg. of vitamin C alone, a second 200 mg. of vitamin P, and the third a combination of 100 mg. of vitamin P and 100 mg. of vitamin C. The group given vitamin C alone showed no improvement in capillary fragility after four months of therapy. The capillary fragility was improved by the vitamin P in both the other two groups. I can supplement these reports from my own experience with rutin. The daily administration of 60 to 120 mg. reduced the bleeding tendency in several patients with liver disease in whom it was previously shown that there was no impairment of the prothrombin function, fibrinogen level or vitamin C status.

Several cases of unexplained bleeding of the gums have been shown to improve and relapse on several occasions as rutin was administered or discontinued.

The minimal requirement for vitamin P has not been determined. In the clinical studies reported above, the dosages have varied from 40 to 300 mg., with an average dosage of 60 to 120 mg. per day. No toxic effects have been reported by any investigators, and as much as 15 gm. has been given orally without any reaction.[218] Sulfonamides were shown by Kushlan[219] to interfere with the efficacy of rutin. As a result, he recommended that, if sulfonamides must be given, the dosage of rutin be doubled or trebled.

Toxicity of Vitamins

Massive supplements of purified vitamins are given too often without concern about any possible toxic effect because it is generally believed that even if the vitamin supplement will do no good, at least it will do no harm. It is fortunate that most vitamins, with the exception of vitamin D, have such a low level of toxicity that the LD_{50} for animals is in the range of several hundred milligrams per kilogram of body weight. Nevertheless, there are enough scattered reports of toxic manifestations from the use of various vitamins to make one pause before employing the large doses of vitamins that are sometimes given.

It has long been known among Arctic explorers that the ingestion of polar-bear liver will cause a serious illness, and this has been recently explained by demonstration of an excessive vitamin A content of the polar-bear liver. Wolbach[220] studied the effect of excessive amounts of vitamin A upon animals. When 1000 or more international units of vitamin A per gram of body weight was given, absorption of bone occurred, with resulting fractures. There were also weight loss, skin lesions, liver damage due to excessive storing of fat and an increase in the size of the adrenal glands.[220] Several reports of toxic manifestations in human beings have appeared in the literature. In 3 young children who had received doses in excess of 100,000 international units per day over a long period, the outstanding clinical features were anorexia, irritability, bone pain, dry, cracked lips, sparse, coarse hair and hepatomegaly. X-ray studies of the bones showed periosteal proliferation not unlike that seen with scurvy. The children all recovered when vitamin A supplementation was discontinued.[221, 222] An adult who had taken 6,000,000 units of vitamin A for five successive days was reported to show vertigo, headache, vomiting, excitation and gastric irritability.[223]

The B complex has exhibited relatively few manifestations of toxicity. Among several reports of sudden death following the intravenous injection of thiamine is that of Reingold and Webb,[224] who described a sudden death after the fourth intravenous injection of thiamine that they believed to be due to anaphylaxis. Because of the possibility of sensitivity to thiamine, the intravenous use of this vitamin represents a potential hazard.[225]

Powers[226] reported circulatory collapse after the intravenous injection of approximately 30 mg. of niacin, and 2 similar cases were described by Pelner.[227] A scaly, follicular dermatitis has been observed to occur during the use of pyridoxine in the treatment of radiation sickness.[124] The dermatitis disappeared upon withdrawal of the vitamin and recurred with resumption of pyridoxine therapy. Para-aminobenzoic acid may cause acidosis, leukopenia and abdominal distention, according to Ravenel.[133] In addition to the leukopenia previously mentioned, Zarafonetis[138] reported such toxic manifestations as drug fever, dermatitis medicamentosa, nausea, vomiting and a fatal case of toxic hepatitis. Transient vertigo, syncope and headache were occasionally observed after the intravenous administration of 150 mg. of folic acid, a procedure that has now become obsolete.[228] To complete the summary of ill effects from the vitamin B complex, the observation of Alvarez[229] is well worth emphasis — namely, that in some people with unexplained abdominal cramps, the cause will be found to be vitamin capsules and the patients will have relief when the vitamin supplements are discontinued.

To judge from the numerous reports, the toxic manifestations resulting from large doses of vitamin D must be well known. Of all of the vitamins, this is potentially the most toxic, and the enthusiastic reports of benefit, either real or fancied, in the treatment of arthritis and certain skin diseases have led to the ingestion of tremendous quantities of vitamin D. Anning et al.[230] observed toxic symptoms in 19 per cent of 200 patients who had received daily doses averaging 100,000 to 150,000 units. The symptoms of vitamin D toxicity include anorexia, nausea and vomiting, diarrhea,

polyuria, muscular weakness, lassitude and headache. These represent earlier symptoms and are a warning to discontinue the drug.[231] More serious results of vitamin D intoxication include metastatic tissue calcification, renal insufficiency and death.[231-233] In general, the toxic symptoms of vitamin D poisoning are associated with a rise in serum calcium, but toxic manifestations are also found without any evidence of serum calcium elevation.[147] This suggests that vitamin D itself is toxic, aside from its effect upon calcium metabolism. It is safe to assume that any dose greater than 50,000 units per day is potentially dangerous. A high milk consumption may potentiate the toxicity of vitamin D, and the use of vitamin D is contraindicated in cases of arteriosclerosis, hypertension and renal disease.[232, 234] Treatment for vitamin D intoxication includes withdrawal of the medication, elimination of milk from the diet and liberal administration of physiologic saline solution intravenously.[235]

As for the other fat-soluble vitamins, large doses of vitamin E caused headaches, dizziness and vertigo,[161] and such symptoms as a sensation of heat, tingling, headache and tinnitus were temporary ill effects in some patients who received 100 mg. of Synkavite or 180 mg. of Hykinone intravenously.[236]

In view of these toxic manifestations, although an infrequent occurrence with some of the vitamins, the promiscuous use of massive doses of purified vitamins is not considered justified on the grounds "that they cannot do harm." Another ill effect, although not actually toxicity, from the use of large doses of purified vitamins is the appearance of deficiency manifestations that are believed to be on the basis of vitamin imbalance. This subject is discussed further below.

Antivitamins and Vitamin Imbalance

As a conclusion to this review of the therapeutic uses of vitamin supplements, it is worth while to consider briefly the investigations of antivitamins and vitamin imbalance that may produce a "conditioned" vitamin deficiency.

An antivitamin is defined in an excellent review by Wright[9] as any substance that interferes with the synthesis or metabolism of a vitamin. This interference may be due to inactivation or destruction of the vitamin or an irreversible combination between the vitamin and the antivitamin. In most cases, however, the antivitamin functions as a competitive inhibitor — that is, it is a substance that is so nearly similar in chemical structure to the vitamin that it can enter into biologic systems in place of the vitamin, but is physiologically inactive. The effect of the vitamin antagonist is dependent upon the ratio of the quantity of the analogue to that of the vitamin.[237] The inhibitory effect of the antivitamin can be abolished if there is a sufficient supply of the vitamin in question, apparently because there may be a greater natural affinity of the cellular enzyme system for the vitamin.

The original observation that suggested the possibility of antivitamins is the well known antagonism of paraminobenzoic acid and sulfonamide. It is through the study of bacterial nutrition that many of the vitamin-antivitamin relations have been elucidated. In this way, the search for antivitamins aids in the development of chemotherapeutic compounds. Conversely, antivitamins, by blocking enzyme systems, may be used in establishing the role of various vitamins in metabolism.

In Wright's[9] review most of the antivitamins mentioned were synthetic products and were primarily research tools.

So far, very few antivitamins have been discovered in food, but the demonstration of an antiniacin compound in corn[238] lends support to the earlier postulation that pellagra was due to the toxic effect of corn and explains why there was an absence of pellagra in persons living on diets that contained much less niacin than those of corn eaters who developed pellagra. The isolation of another natural analogue, the hemorrhagic agent of sweet-clover disease,[239] made it possible to discover vitamin K. Natural antivitamins for thiamine[240] and biotin[241] have been isolated. The antithiamine content of certain raw fish may produce thiamin deficiency in man.[242]

More recently, certain synthetic antivitamins have offered a ray of hope in the treatment of cancer. The most promising of these to date are the folic acid antagonists, of which the best known is aminopterin.[243]

It is theoretically possible for chemotherapeutic agents (antivitamins) to enter into enzyme systems in man and thus to manifest a "conditioned" vitamin deficiency.[9] Whether antivitamins, through their effect upon intestinal synthesis of vitamins, can cause vitamin deficiency in man is open to question; but positive proof of such an effect has not been produced as yet.[9]

The literature on antivitamins is voluminous. In this review, discussion is limited to a mere indication of such aspects of antivitamins as are contingent upon the therapeutic use of vitamins.

Attention has been directed occasionally to the concept of vitamin imbalance,[244-246] a concept that is a strong argument against the use of purified vitamin supplements, particularly the members of the vitamin B complex. When pellagrins were given niacin, they often showed signs of riboflavin or thiamine deficiency.[244, 246] It was said that niacin "unmasked" the other deficiencies and that most deficiency diseases were multiple. A more probable explanation of this phenomenon is that the use of supplements of niacin increased the

demand for riboflavin or thiamine in a person who was in a borderline state of nutrition with respect to the latter.

Animal experimentation has suggested two other mechanisms for the production of "conditioned" vitamin deficiencies by the use of large doses of one or two purified vitamins. Antagonism between members of the vitamin B complex was offered by Richards[246] to explain the development of pyridoxine deficiency in rats given large amounts of thiamine. Supplee et al.[247] demonstrated that administration of thiamine and pantothenic acid caused an increased urinary excretion of riboflavin.

Reports of some clinical evidence of vitamin imbalance have been reviewed by Richards.[246] A case of ariboflavinosis that developed after lengthy treatment with thiamine is described by Gripwall.[6] The "burning-feet" syndrome and the leg pains of subjects experimentally deficient in vitamins were made worse when the patients were given purified supplements of the better known members of the vitamin B complex, but were relieved when the patients were fed a luxurious diet or given the whole vitamin B complex in the form of yeast.[24, 25] I have observed several cases in which glossitis and cheilosis developed while the patients were receiving large doses of thiamine, riboflavin and niacin, and in which "cures" were obtained by discontinuance of the vitamin supplements. Creation of a vitamin imbalance is the probable basis for the ill effect of folic acid on the central nervous system.[188]

These observations suggest a need for caution in the use of large doses of purified vitamin supplements, especially in patients who are in a state of subclinical deficiency.

Summary and Conclusions

The need for the widespread consumption of purified vitamin supplements is questioned. A critical review of the current vitamin literature shows that the minimal requirements for the vitamins essential to man are much less than the Recommended Dietary Allowances. Vitamin-deficiency states are now infrequent in the United States. The lack of objective evidence of any improvement in health, fitness or work capacity of large population groups who received purified vitamin supplements suggests that the average American diet is adequate enough to prevent subclinical vitamin deficiency. Many of the so-called signs of vitamin deficiency are nonspecific and are not alleviated by vitamin supplementation. The use of vitamins as supportive therapy in infections and chronic diseases is largely empiric. Therefore, there seems to be little need for vitamin supplements from the nutritional standpoint.

Although many claims for the therapeutic value of vitamins in certain pathologic states will not withstand the test of controlled study, there are some conditions in which a specific vitamin has value by virtue of its pharmacologic properties.

Not only is the administration of large doses of purified vitamins often wasteful and foolish, but also serious consideration must be given to the possibility of a toxic effect or the development of a vitamin imbalance.

If a definite state of avitaminosis exists, long-term use of vitamin supplements is unnecessary. The best suggestion is that of Cowgill to "vitaminize" the patient for a few days with three to five times the requirements and then establish him on a good diet.

In conclusion, I believe that if a person takes a good diet, he will not benefit from vitamin supplements, and that if the patient does not take an adequate diet, the treatment is a good diet, not vitamins.

I am indebted to Miss Kate Spencer, who devoted many long hours to searching through the medical literature for articles on vitamins.

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Correction. In the Medical Progress report by Dr. George W. Thorn and his associates entitled "Studies on the Relation of Pituitary-Adrenal Function to Rheumatic Disease," which appeared in the October 6 issue of the *Journal*, the last six words in the final sentence of the first paragraph on page 536 should be changed to read "a finding recently confirmed in further experiments.[26]"

NEW HAMPSHIRE MEDICAL SOCIETY

PROCEEDINGS OF THE ONE HUNDRED AND FIFTY-EIGHTH ANNIVERSARY (Concluded)

House of Delegates, June 13, 14 and 15, 1949

Dr. Crisp referred to a communication from the president of the New Hampshire Pharmaceutical Association, registering a protest against dispensing of drugs by physicians in groups. This matter had been discussed at the annual meeting of the Association, which also protested against the employment of pharmacists by physicians, private ownership and so forth.

The Secretary stated that his impression was that the druggists objected to the fact that doctors were passing out pills to their patients, and not writing prescriptions.

Dr. Crisp replied that the druggists were also against the establishment of dispensing pharmacies employing pharmacists, and run by doctors.

Dr. Gifford stated that several pharmacists had informed him that physicians have had their own dispensaries within the particular group, and that the patient must go there to get his medicine.

Dr. Bowler said that he assumed that the protest was not aimed at the individual physician dispensing in his own office, which would be ridiculous. His group, however, would be interested in the development by hospitals of their own pharmacies, in the future, perhaps, because that had become an established method for some time.

President Dunbar referred to correspondence with Mr. Smith, who was wholeheartedly with the medical profession in its campaign against socialized medicine and who had even sent his personal check as a contribution to the campaign. Dr. Dunbar knew of only one clinic in the State that operated a drugstore, in the Winnepesaukee area.

Dr. Walck was of the opinion that the medical profession should encourage all possible support from the pharmacists. Mr. Smith had been one of the most energetic workers in Strafford County co-operating with the Committee and appeared to be wholeheartedly behind the whole program against socialized medicine.

Dr. Jessup stated that the protest appeared to be directed largely against his group. He asked what the basic objection of the pharmacists was, since his group did not dispense but hired two fully qualified pharmacists to do all the work. The group had noted that a large percentage of patients did not use its own pharmacy. Prescriptions that could not be filled in pharmacies within the State were not used. The system had originally been started, in part at least, to facilitate the dispensing of medicines to patients, which all physicians do to some extent. Originally, it had been meant to be a small drug room, and since there were eleven or twelve doctors in the group, it seemed more to the point to consolidate the drugs in one room, rather than to have twelve dispensaries. It was a regularly chartered drugstore, with its own bookkeeping and is separated from the group. The building was owned by the clinic group.

Secretary Metcalf asked if that was the group in Laconia. Dr. Walck replied that it was.

Dr. Bowler moved that the protest be referred to the Committee on Public Relations.

This motion was duly seconded and was carried.

President Dunbar moved that the Committee on Public Relations give consideration to the organization of state-wide or local health conferences of doctors, laymen and consumers, similar to the conference held in Massachusetts last February.

This motion was duly seconded and was carried.

President Dunbar also moved that the Society participate in the Conference of Presidents, and that the House ratify the payment of $10.00 for this purpose.

This motion was duly seconded and was carried.

President Dunbar then moved that the House of Delegates pass a resolution against compulsory health insurance, as follows:

> WHEREAS, under a system of free enterprise and personal initiative, the American Medical profession has attained for the people of these United States the highest standards of scientific performance, treatment and research to be found in the world; and
>
> WHEREAS, there exists in many forms voluntary health insurance whereby payments for health care may be effected on a purely voluntary budgetary basis; and
>
> WHEREAS, under voluntary health care programs the people of this country are left free to select their physicians and hospitals and to carry such voluntary health insurance as they may wish; and
>
> WHEREAS, under compulsory health insurance employes, employers and the self-employed, as well as those in other categories, would be faced with a compulsory tax on annual income, earning power or wages to support a governmentally controlled medical program; and
>
> WHEREAS, the experience of all nations where government has assumed control of medical services has shown that there has been a gradual erosion of free enterprise and a progressive deterioration of medical standards and medical care to the detriment of the health of the people,
>
> NOW, THEREFORE, BE IT RESOLVED, that the New Hampshire Medical Society does hereby go on record against any form of compulsory health insurance or any system of politically controlled medicine, firm in its belief that the American tradition of free enterprise may best be carried out by the people and for the people through voluntary means; and that a copy of this resolution be forwarded to the president of the United States and to Senators Styles Bridges and Charles W. Tobey and to Congressmen Chester E. Merrow and Norris Cotton repre-

senting the state of New Hampshire in the National Congress, and that they be urged and respectfully requested to use every effort at their command to prevent the enactment of compulsory health insurance legislation.

This motion was duly seconded and was carried.

President Dunbar then stated that the Society needed organization, which would cost money. The problem was how to raise that money. Should the Society raise its dues to a certain amount, and fit the services to that amount? Or should it consider the services that it must have and make the dues fit the services?

Next to be considered was the cost of employing the Woodbury firm. Their budget called for $14,391, but it was possible that some donations might be obtained to cover some of that, which would only make it necessary for the Society to raise $6,891. Also, the matter of employing a lay assistant to the Secretary should be considered. That matter would have to be taken up by the next president and the Committee on Public Relations.

It had been suggested that New Hampshire organize with Vermont and Maine, and it would take time to organize a system of that kind. The cost of such a program could not be estimated.

Dr. Bowler moved that the dues be increased to $40 a year.

The motion was duly seconded.

Dr. Bowler then spoke as follows:

It is quite certain that the circle in the budget has to be cut into at some point. The question of the expenditure side of that budget is so undeterminable at the present time that it is impossible to estimate it accurately. The items that we know are the campaign, which you heard Dr. Dunbar say is in the neighborhood of $15,000. There may be some offsets or some transfers that can be worked out during the year with other organizations. However, that does not seem to be a good basis for the budget. So that probably, at least at this point, it ought not to be considered as ours.

The next large question is the question of the full-time executive secretary, which was discussed last evening. The possibilities are quite wide and quite unknown or unexplored.

Dr. Metcalf has said in his letter that the imposition of the Society on the willingness, charity and energy of one person regarding the work to be done is absurd.

We are in a situation today that is bound to mean more work. Speaking of the load, I hope that Dr. Metcalf's letter can be tabled to the point where he will continue until this program is approved and worked out. There are possibilities of a tri-state program, and it might be something that the Society would be interested in.

We have been running on a tin-horn budget, as we all know, for some time, and now we are at the point where we shall have to do one thing or the other.

My motion for the dues of $40 a year may seem to have been picked out of the air, and it is, to some extent, but if you look at it, it adds up to an income of around $25,000. But, it is not a lot of money in terms of the items we shall have to account for.

Dr. Feiner stated that Dr. Dunbar had mentioned that the budget was about $14,000 for public relations, and any efficient secretary would require a minimum salary of $4000 or $5000 a year, which would make a total of $19,000. He did not know just what the total of paying members was.

Secretary Metcalf replied that it was about 600.

Dr. Feiner then observed $30 per member would be required for that one item of expense. He did not think that even $35 was sufficient. He did not consider it too much to raise the dues to at least $45 or even $50 a year, rather than have to ask for more money again. He therefore moved that Dr. Bowler's motion be amended so that the dues would be $50 a year.

Dr. Brown asked how much the American Medical Association would want next year.

Dr. D. G. Smith answered that Dr. Lull had said he thought there would be no assessment in 1950. To date, about $2,000,000 had been collected, and Dr. Lull did not believe that there would be an assessment in 1950.

The motion of Dr. Bowler that the dues be raised to $40 was duly seconded and was carried unanimously.

Dr. Dye then proposed that the following amendment to Chapter X, Section 1, of the Constitution and By-laws be laid on the table: "An assessment of $40 per capita on the membership of the component societies is hereby made the annual dues of this society." After further discussion the motion was amended to read: "The House of Delegates shall determine the amount of the annual dues." The motion was laid on the table.

Dr. Holyoke then spoke as follows:

I was asked by the Society of Clinical Pathologists of the State to present what we know are some of the problems that will come up in connection with blood banking in the State in the near future.

Of course, I think the fact that you passed a resolution last night indicates that you are aware of some of those problems. First of all, I think that we all agree that the establishment of many blood banks throughout the State is certainly advantageous, in that it makes available to the various hospitals a large supply of blood of various types for immediate use, so that anyone can be given a transfusion.

In 1937 the first blood bank was established. The first banks established were purely hospital banks, to supply a given hospital. Since that time, literally thousands of banks have been established throughout the United States. The present trend is away from a single hospital bank toward a centralized bank. So that in one city, where there are several hospitals, there will be one bank supplying all the hospitals within the community.

There are actually several possibilities whereby that can be brought about. One hospital in the city may set up a bank and supply all other hospitals with blood, and it will be a co-operative effort.

Another effort, perhaps most widely used throughout the United States, is to have the so-called community bank. These banks are usually under the direction of the county medical societies. They supply all the hospitals in a given area with blood.

One other possibility, and the reason why we, in the various county societies in the State, ought to think about the problem, is the establishment of a state-wide Red Cross blood bank. We shall not hear much from the Red Cross for probably a year, because they have their hands full in setting up other banks. But perhaps next year, they will sound out the various county societies and perhaps the state society as to whether it would like to have set up within the State a large blood bank to supply the State with blood.

Their system is to procure the blood and turn it over to the hospitals after it is drawn.

I think that in line with that, it is worth saying that their system of getting donors has worked very well in some locations. The Red Cross blood banks have been a great asset in some communities, and in others, they have not been so good.

In some places, a great stress is still laid on individual use of the blood, and on being morally bound to replace the blood from friends or members of families. Other banks have gone on the basis that the blood is free; it is yours, and you don't have to do anything about it. But I think the Red Cross banks that have had that system have not been a success.

In the State at present, there are only five banks set up. There are a few others in hospitals, which carry a fair supply of blood on the refrigerator shelves, but, it is not a definite thing, so that it would be conceivable that those hospitals might be short of blood.

Two of the banks in the State do make the blood available at times to doctors in surrounding towns or surrounding communities. But we have virtually no community blood banks at the present time in the State.

There is a Red Cross bank in Massachusetts that is functioning and doing, as far as I can tell, a fairly good job. It ought to do a better job, as time goes on.

In Vermont, within the next three or four months, there will be a blood bank set up under the auspices of the Red Cross. This bank is going to supply eastern New York and all of Vermont, and they are ready — if the members of the various county medical societies in New Hampshire wish them to do so — to supply part of the blood to them.

Also, there is in process the setting up of a blood bank for the city of Portland, Maine.

So that we shall have these large banks all around the perimeter of the State.

As to what the banks can do, I think we could sum it up and say that a large blood bank can ensure the people in the neighborhood of an adequate dose of blood. Certainly, it is an efficient way to obtain blood. It is a method whereby small hospitals and small users of blood can have available to them ample supplies of blood.

There is one thing in line with the national policy: it would have set up through the State a number of large blood banks, whereby we shall be able to help each other in times of disaster. Of course, the national Government is thinking a lot about that at the present time.

One other advantage in having a large blood bank is that it makes available to the doctors or the hospitals that are co-operating with the program plasma products, particularly albumin; that is important because the albumin prepared from plasma is virus free, and there is no need to worry about infectious hepatitis, which is becoming a tremendous problem for people using blood in any volume at all, or using blood products.

If you decide that you would like to co-operate with some of the Red Cross Bank programs, remember that must be done through the counties. Red Cross does not establish it anywhere, unless the county medical societies agree to have it done.

This problem will come up next year so that each county society and the State Society may consider and talk about it at the next meeting.

Upon motion duly made, seconded and voted, the second meeting of the House of Delegates adjourned at 10:30 a.m.

The Third Meeting of the House of Delegates was called to order by Speaker Dube at 9:20 a.m. on June 15, 1949.

The following members responded to roll call:

The President, *ex-officio*
The Vice-President, *ex-officio*
The Secretary-Treasurer, *ex-officio*
James Jessup, alternate for Roger Brassard, Laconia
Samuel Feiner, Ashland
W. J. Paul Dye, Wolfeboro
Howard Sawyer, alternate for Francis J. C. Dube
Marjorie A. Parsons, Colebrook
William H. Gifford, Colebrook
Leslie K. Sycamore, Hanover
Reginald K. House, Hanover
Norman W. Crisp, Nashua
Harris E. Powers, Manchester
James B. Woodman, Franklin
Francis Brown, alternate for Warren H. Butterfield
Ellsworth Tracy, alternate for William D. Penhale
Donald W. Leonard, Exeter
Fred Fernald, Nottingham
Edna Walck, Dover
Albert E. Barcomb, Rochester
B. Read Lewin, Claremont
Addison Roe, Newport

Dr. Dye moved that Section 1 of Chapter X of the By-laws, which is headed "Assessments and Expenditures," be amended to read as follows: "The House of Delegates shall determine the dues of members of this Society."

This motion was duly seconded and was carried.

Dr. Bowler then moved that the dues of the New Hampshire Medical Society be $40.

This motion was duly seconded and was carried.

Dr. Leonard, for the Committee on Officers' Reports, moved that the custom of sending delegates from the New Hampshire Medical Society to the annual meetings of the other New England state societies be renewed.

This motion was duly seconded and was carried.

In accordance with the suggestion in the report of the Secretary, he then moved that the Committee on Amendments to the Constitution and By-laws be instructed to prepare an up-to-date copy of the entire Constitution and By-laws, and that the Secretary be authorized to incorporate them in a printed booklet for the reference of the members.

This motion was duly seconded.

Dr. Bowler offered an amendment that, on review and before printing, the copy be submitted to the next House of Delegates.

Dr. Leonard accepted the amendment.

Upon a voice vote, the motion was carried.

Dr. Leonard, for the Committee on Officers' Reports, moved that the *Transactions* be printed in an annual volume, omitting reprints of scientific and other papers presented at the annual meeting, except such essays as are awarded prizes by the Society and any other papers having specific application to the Society. It was also suggested in this motion that publication of the *Transactions* be made within three months of the annual meeting.

Secretary Metcalf remarked that the papers that go into the *Transactions* are printed previously in the *New England Journal of Medicine*, being spread out over a whole year. The papers are kept set up in print and simply transferred to the *Transactions*. In that way, the Society saved about a thousand dollars. If a volume was brought out in three months, the material would have to be specially set, at a cost of $6 apiece.

Dr. Leonard stated that the motion was to omit the scientific papers from the *Transactions*, except the prize essays and those of merit.

Secretary Metcalf then pointed out the advantages of having the *New England Journal of Medicine* handle the publication, which was a big job. If the Publication Committee had to take over that work in three months, he would certainly resign from the Committee.

Dr. Leonard withdrew the sentence referring to the suggestion of publishing the *Transactions* within three months.

Speaker Dube suggested that the matter be referred to the Publications Committee, of which the Secretary was the chairman.

The Secretary stated that certain portions of the book were valuable. The account of these meetings held in the last three days, the committee reports, the list of members, the obituaries, and other phases might be occasionally used.

Dr. Bowler stated that he was in favor of supporting the continuance of the *Transactions*, if only for the historical value, and he moved the question.

Dr. Leonard's motion was then read, excluding the suggestion that the transactions be published within three months.

Secretary Metcalf stated the present cost of the books was $3 a volume; 660 copies had been received this year, at a cost, roughly, of $2000.

Speaker Dube asked those in favor of the motion to signify assent by raising their right hands.

There were 13 "No" votes, and the motion was lost.

Dr. Leonard, in accordance with the suggestion of the Delegate to the American Medical Association, moved that the term of the Delegates of the New Hampshire Medical Society begin on January 1 of the year after his election.

This motion was duly seconded and was carried.

Dr. Leonard, also in response to the suggestion of the Delegate to the American Medical Association, moved that the New Hampshire Medical Society co-operate with the American Medical Association by requesting each county society to submit the name of one of its members as the "outstanding general practitioner of the year."

This motion was duly seconded, and was carried.

Dr. Leonard, as a delegate from Rockingham County, presented the name of Dr. Cleon W. Colby for life membership.

This motion was duly seconded and was carried.

The financial report of the Trustees was then presented as follows:

JANUARY 1–DECEMBER 31, 1948

GENERAL FUND

Receipts:			
Balance on hand January 1, 1948	$2,764.60		
Nashua Trust Company	Int. 11.41		
Portsmouth Tr. & Guarantee	Int. 36.44		
New Hampshire Savings	Int. 21.32		
United States Series G Bonds	Int. 100.00		
Total		$2,933.77	
Expenditures:			
Cash balance December 31, 1948			$2,933.77
United States Series G Bonds			5,000.00
Total			$7,933.77

BARTLETT FUND

Receipts:			
Balance on hand January 1, 1948	$2,259.75		
Portsmouth Savings Bank	Int. 69.54		
United States Series G Bonds	Int. 75.00		
Cash Balance December 31, 1948			2,404.29
United States Series G Bonds			2,000.00
Total			$4,404.29

PRAY FUND

Receipts:			
Balance on hand January 1, 1948	$319.33		
Strafford Savings Bank	Int. 5.53		
United States Series G Bond	Int. 25.00		
Total		349.86	
Expenditures:			
Essay Prize		0	
Cash Balance December 31, 1948			349.86
United States Series G Bonds			1,000.00
Total			$1,349.86

BURNHAM FUND

Receipts:			
Balance on hand January 1, 1948	$1,091.81		
New Hampshire Savings Bank	Int. 27.62		
United States Series G Bond	Int. 25.00		
Total		$1,144.43	
Expenditures:			
Essay Prize		0	
Cash Balance December 31, 1948			1,144.43
United States Series G Bonds			1,000.00
Total			$2,144.43

BENEVOLENCE FUND

Receipts:			
Balance on hand January 1, 1948	$3,895.60		
New Hampshire Savings Bank	Int. 98.93		
United States Series G Bonds	Int. 75.00		
Dr. C. R. Metcalf	35.00		
Total Receipts & Cash Balance, December 31, 1948			4,104.53
United States Series G Bonds			3,000.00
Total			$7,104.53

Dr. George C. Wilkins then spoke as follows:

I should like to have the privilege of speaking for the Board of Trustees about the Benevolence Fund, which was started in 1931, and discussed at the meeting Monday afternoon. That fund was started with the idea of building up a fund sufficient to give an income to help out any indigent physician in the Society.

At first, we took $1 from each person's subscription, and that was allocated to the Fund. That was cut down to fifty cents, and then it was cut down to nothing. We have had no income except from the invested funds and from a very small contribution of $25 to $50 from the auxiliaries of three different county societies.

Twice within the last two years, I have been asked if some money was available to help out an indigent physician who has come upon hard times and was unable to do anything about it. However, we cannot use the principal. We only have $7104 at the present time.

The Trustees would like very much to have the $1 portion of the dues set aside for the Benevolence Fund, in order to build it up to a point where we could use the income to help someone out.

These cases do not come up very often, but when they do, it is rather a sad position for us to be in, to say that we cannot do anything to help them. Therefore, the Trustees would like very much to have that allocation made to the Benevolence Fund, if the House of Delegates believes that it should be done.

Dr. Bowler moved that the question be referred to the budget committee for next year.

Speaker Dube stated that there was no budget committee.

Dr. Bowler replied that, temporarily, the officers could be used as such. They would look over the budget, on the basis of the new dues, the campaign work, the question of the new executive secretary and so forth.

Secretary Metcalf remarked that the Trustees were responsible for the invested funds, and that the Treasurer acted as a budget committee, paying out the necessary expenses. The present rule was that nobody could spend any money unless the House gave its approval, so that the budget committee would be purely advisory.

Dr. Bowler stated that the budget had to be set up. He assumed that a special meeting of the House would be called as early as these things were in shape to be recommended; meanwhile, work must be done.

Dr. Feiner asked if it had to be a standing committee. If not, the by-laws would not have to be changed, because a special committee could be appointed by the Chairman, to report back at the next meeting of the House of Delegates.

Dr. Bowler stated that at present there was no budget committee as an officers' committee. But, in the meantime, he supposed that the matter had to be handled by the officers in this preliminary work with the budget.

Dr. Wilkins remarked that the request of the Trustees could only be granted by a vote of the House of Delegates.

Dr. Crisp asked how much was needed to put the fund in working order.

Dr. Wilkins replied that, originally, the plan had been that after the fund had reached $10,000 the income could be used for any such purpose, and if the income from the fund was not used, it could be added to the principal. Of course the income from $10,000 was not too much, and it would not go very far, but the fund should be that amount before any of the interest was taken away.

Dr. Bowler re-phrased his motion to state that this item be referred to a committee to be appointed by the President, to be considered along with a study of the budget, the recommendations to be reported to the next meeting of the House of Delegates, and that Dr. Wilkins's recommendation be referred to this Committee.

This motion was duly seconded and was carried.

President Dunbar then moved that the House of Delegates go on record as being in sympathy with the objectives of the American Diabetes Association, — that is, to improve the treatment of diabetes, to bring the newest knowledge of the disease to all physicians, to encourage and support research in the field and to increase knowledge of diabetes among the general public, — that the incoming president appoint a diabetes committee of three to aid in this program and, that the Secretary inform the county societies of this action, recommending that each appoint a diabetes committee.

This motion was duly seconded and was carried.

Dr. Sycamore moved that a vote of appreciation be extended to Dr. Dunbar for the time and effort that he had put into the service of the Society during this past year, and for the inspiring leadership he had given.

This motion was duly seconded and was carried.

Dr. Sycamore then made a similar motion with reference to the Secretary-Treasurer.

This motion was duly seconded and was carried.

Speaker Dube stated that the next item of business was the selection of a place for the next annual meeting.

Dr. Bowler stated that he had been asked a year ago whether Hanover would be interested in having the Society next year. This would not be practical because of the so-called Hanover Holiday, which is the week between commencement and reunion. However, he suggested that Hanover be considered for the following year. He moved that Newcastle be chosen for 1950.

Dr. Dye seconded the motion.

Dr. Gifford suggested the Mount Washington Hotel, which had adequate floor space for the exhibits. This might inconvenience the physicians in the cities, who like to be able to dash in and see their patients and dash back to the meetings and catch a lecture or see what is going on.

Dr. Barcomb seconded Dr. Gifford's suggestion.

Dr. Dye stated that the exhibits brought in a certain amount of income, and the Mount Washington Hotel had stated that they would be delighted to have the Society meet there, and also that they had adequate space and facilities for all the exhibits.

Speaker Dube stated the motion that the Society meet at the Wentworth Hotel in Newcastle next year.

Dr. Dye seconded a motion by Dr. Bowler that the members be polled by postal card, and amended that motion so that the officers of the Society would be empowered to act with reference to the final selection of the site.

Dr. Bowler accepted the amendment.

Speaker Dube stated the motion before the House that the Secretary poll the Society, and that the officers be empowered to act upon the result of the poll, to select the future place of meeting next year. He asked all those in favor of this motion to signify assent by saying "aye."

There was a chorus of "ayes," with one dissenting "no," and the motion was carried.

Dr. Bowler then moved that the continuance of Mr. Woodbury's services be approved, pending the report of the Budget Committee.

This motion was duly seconded and was carried.

Dr. Feiner recommended that at the next year's meeting, the House of Delegate's meetings be started on a Sunday, so that the bulk of the business could be finished before the scientific sessions began.

Dr. Dye moved that the House adjourn.

This motion was duly seconded and was carried.

Whereupon, the third meeting of the House of Delegates was adjourned at 11 o'clock in the forenoon.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

BENJAMIN CASTLEMAN, M.D., *Associate Editor*

EDITH E. PARRIS, *Assistant Editor*

CASE 35521

PRESENTATION OF CASE

A sixty-two-year-old woman was admitted to the hospital for the fourth time with a complaint of coma following epileptic seizures.

The patient had had recurrent epileptic seizures for about fifteen years. These attacks were variable in frequency, duration and nature, and recurred at any time of day or night. In some of them she was able to carry out co-ordinated motor activity in an automatic way for a few minutes to an hour or more while seemingly "in a daze." In others, she suddenly lost consciousness without warning and fell to the ground, where she lay motionless for a few minutes, sometimes with urinary incontinence. Rarely, there were tonic-clonic convulsions, with tongue biting. Some of the attacks were heralded by peculiar unlocalized "crawling" sensations in various parts of her body, often in the back of her neck. In all of them, there was total amnesia for the attack itself. These attacks occurred anywhere from once in two or three months to three or four times a week. Over the course of the years, she received many forms of anticonvulsant medication, which never controlled her seizures satisfactorily. Repeated electroencephalograms showed diffuse abnormalities consistent with epilepsy. Radiograms were normal except for osteoporosis of the left posterior clinoid process. Lumbar punctures were normal, and the neurologic findings were negative. During the six months before admission, in addition to her previous attacks, she began having more frequent episodes of unresponsiveness and unconsciousness between meals, lasting up to three hours at a time, during which she was sometimes noisy and restless. They became progressively more severe and occurred at least three times daily, always occurring between meals or between supper and bedtime.

Physical examination revealed an obese woman, who was dazed and confused. There were a number of cutaneous scars from previous injuries and burns. The remainder of the physical examination and the neurologic examination were negative.

The temperature was 99°F., the pulse 82, and the respirations 20. The blood pressure was 120 systolic, 70 diastolic.

Examination of the blood showed a hemoglobin of 12 gm. and a white-cell count of 14,670, with a normal differential. Urinalysis was normal. A fasting blood sugar was 47 mg. per 100 cc.; a repeat test on the following day was 35 mg. per 100 cc. The nonprotein nitrogen was 21 mg., the calcium 9.4 mg., and the potassium 4.6 mg. per 100 cc. The sodium was 141 milliequiv., and the chloride 105 milliequiv. per liter. The carbon dioxide was 29.4 milliequiv. per liter. A cephalin-flocculation test was negative in twenty-four and forty-eight hours. The total protein was 6.49 gm. per 100 cc., with 4.43 gm. of albumin and 2.06 gm. of globulin. The bromsulfalein test showed 16 per cent retention of the dye. The phosphorus was 3.7 mg. per 100 cc. A blood Hinton test was negative.

A glucose tolerance test revealed a high value of 208 mg. per 100 cc. in two hours and a low value of 58 mg. in six hours. The response of the patient, with a fasting blood sugar of 47 mg. per 100 cc., to an injection of 0.01 cc. of epinephrine (in a dilution of 1:1000) per kilogram of body weight was 54 mg. per 100 cc. in fifteen minutes and 39 mg. in sixty minutes.

The patient was fasted for twenty-four hours, at which time a convulsion occurred. A blood sugar determination at this time was 45 mg. per 100 cc. She responded immediately to intravenous glucose therapy.

Two weeks after admission an operation was performed.

Differential Diagnosis

Dr. Earle M. Chapman*: It seems clear from the history and data presented that this patient suffered from hypoglycemia. That is a positive clinical diagnosis.

What are the main causes of hypoglycemia? There may be four main causes, and it is for us to go through them to determine which seems most likely to fit this patient. First, I think we have to consider abnormality of the liver cells. If a failure of gluconeogenesis in the liver takes place, hypoglycemia can occur. Did this patient have enough evidence to support a diagnosis of severe liver disease to explain this syndrome? When a normal liver is removed profound hypoglycemia may result, but 80 per cent must be removed before hypoglycemia is produced. So I cannot believe that the evidence here indicates that 80 per cent of this patient's liver was impaired. All the liver-function studies were normal, with the single exception of 16 per cent retention of bromsulfalein. I am inclined to discount this as one of the minor variations in laboratory data that tend to confuse one.

Secondly, I think a decreased gluconeogenesis can result from diminishing output of anterior pituitary hormone, thyroid hormone or cortical or medullary secretions of the adrenal gland. On review of the data, there is no evidence on which I can base a diagnosis of endocrine disease of the pituitary, thyroid or adrenal glands. It is true that the basal metabolic rate is not reported. It is likewise true that x-ray examination disclosed some osteoporosis of the posterior clinoid process. I will have to depend on Dr. Wyman to tell me whether he thinks there is a significant abnormality in the region of the pituitary body.

Dr. Stanley M. Wyman: I do not believe that the skull films are definitely abnormal for a person of this age. Osteoporosis of the posterior clinoids seems to be rather general, and there is no evidence of erosion and no evidence of increase in size of the sella turcica. Otherwise, the bones of the skull appear within normal limits. I should be inclined to discount the reported osteoporosis of the clinoids. There are other films available that you may like to see. The films of the chest are grossly unsatisfactory; they are examinations of a heavy person taken with a portable machine. They do show tortuosity of the aorta but no other definitely localized intrinsic disease. In the one film of the abdomen the liver shadow appears to be within normal limits in size and shape. The kidneys are well seen and appear normal; the left lies lower than usual. There are no masses above it, however.

Dr. Chapman: I will accept your word that there is little or no evidence for pituitary disease in the x-ray films.

*Associate physician, Massachusetts General Hospital.

A third cause of hypoglycemia is that produced by long-endured or violent exercise. Occasionally, severe and prolonged exercise will produce hypoglycemia. I have seen one such case in a young boy who did very hard work over a long period and had a fainting spell in which we established the diagnosis of hypoglycemia and he recovered immediately. I would like to read from an article by Romano[1] that bears on this point of attacks of low blood sugar occurring after violent exertion:

> The day following the New England hurricane in September, 1938, he engaged in a kind of wood-chopping contest with a number of neighbors who were clearing fallen timber from their property. After some fifteen minutes of vigorous chopping, he suddenly clutched his axe menacingly, and with a dazed and glassy-eyed expression, wandered about the neighborhood, terrifying people. He was again taken to the Peter Bent Brigham Hospital, where house officers were struck by his confusion, mumbling speech and constant grotesque, ataxic and purposeless movements. Convinced of the hysterical character of his disorder, house officers sprayed a fine stream of ethyl chloride on his bare abdomen to startle him out of his attack. He appeared to respond promptly to this interesting therapy, for he came to himself immediately. He professed amnesia for the entire episode, and the diagnosis of hysteria seemed definitely confirmed. (The probable effectiveness of a large glass of ginger ale, which the patient had been persuaded to drink just before the ethyl chloride treatment, was not appreciated.)

This patient was subsequently proved to have periodic hypoglycemia.

This leads me to the fourth possibility and the one that probably explains this patient's condition which was followed for over fifteen years in our Out Patient Department — the inhibitory action of insulin on the gluconeogenesis of the liver itself; in other words, hyperinsulinism. The history is typical of hyperinsulinism. The data of low blood sugar and response to epinephrine are characteristic, and, in the end, an operation was performed. My guess is that the abdomen was explored and that possibly an islet-cell tumor of the pancreas was discovered and if an enlarged pancreas was found, a subtotal resection was performed. I remember a case in Baltimore seen by Dr. Edward Jarrett, in which an extremely large pancreas was discovered, and the surgeon held it up and said: "How much will we take off?" And he said: "Oh, about there," and they chopped it off about "there," and the patient had no more attacks. No islet-cell tumor was discovered in that case. It would be helpful if they discovered a tumor in the case under discussion.

There are four types of islet cells, and the beta cells that occupy the periphery are smaller than the others and are considered the producers of antidiabetic hormones.

This case illustrates another point to me: the need of a method to determine the level of blood insulin. When I visited the Banting Institute last spring, I was impressed with the amount of intensive work going on in this problem. Dr. Best is devoting a good share of his efforts in working out a practical

method of determining blood insulin. In the case under discussion it would be most helpful in eliminating an erroneous diagnosis that could arise from misinterpretation of spells that seem to have been epileptic or neurotic.

Dr. Robert S. Schwab: This electroencephalogram was taken before the operation and shows marked abnormalities that are underlined with pencil (Fig. 1). We have evidence of localization in the right temporal region because of the large spikes

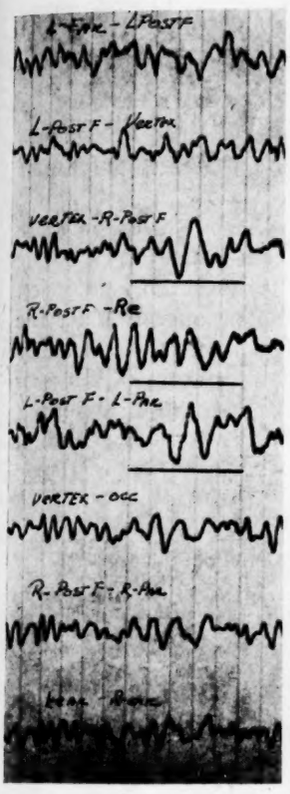

Figure 1.

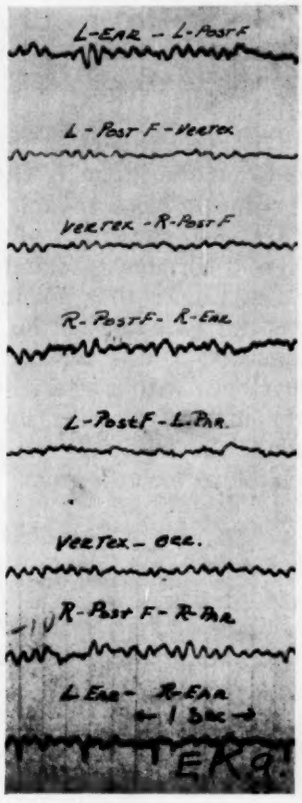

Figure 2.

in the basal lead. Here is a normal electroencephalogram for comparison (Fig. 2).

Clinical Diagnosis

Islet-cell adenoma of pancreas.

Dr. Chapman's Diagnosis

Islet-cell adenoma of pancreas.

Anatomical Diagnoses

Islet-cell adenoma of pancreas.
Epilepsy.
Carcinoma of thyroid gland.

Pathological Discussion

Dr. Oliver Cope: We reached the same diagnosis that Dr. Chapman did and, accordingly, opened the abdomen and looked at the pancreas. It was large and lobular, and no definite tumor was seen or felt. It looked a little bit larger than the normal pancreas. The woman was very obese, and the pancreas felt big and fat. I excised the tail and body of the pancreas down to the neck, leaving head and neck. After excision we incised the specimen longitudinally, starting at the tail and cutting into each lobule as we slit it down. There was one little lobule in the mid-body that looked like the rest but that, when cut into, proved to be a little adenoma; I had taken out more than was needed. The tumor was characteristic; it was the size of a small, seedless green grape, not as big as 2 cm. in diameter. It was well circumscribed and of firm whitish tissue.

My face was scarlet red about this patient. She had been cared for by the Burn Service during the war, and we, like the neurologists, had failed to make the diagnosis. She had made many trips to this hospital, many electroencephalograms had been done, and she had seen many doctors. It was not until Dr. Balboni saw her at home in an attack that suspicion was aroused as to what was wrong. He thought it was not an ordinary seizure and sent her in with the diagnosis of hyperinsulinism and said, "Please determine the blood sugar." He was convinced about the diagnosis. The patient was sent home, however, without a blood sugar determination, and two days later he sent her back and said, "Please do a blood sugar determination" (I do not think he said "please" the second time). What interested me was that many had seen this patient, and many noted that she suffered from a state of confusion, and yet the attack was never classified until Dr. Balboni looked at the patient and said, "This is not an ordinary epileptiform seizure."

Dr. Schwab: The postoperative electroencephalogram was exactly the same as the preoperative. I would like to ask Dr. Chapman how he explains the persistence of epileptic waves after removal of an islet-cell adenoma of the pancreas.

Dr. Chapman: That is interesting because I think it happened in a patient who had, perhaps, a fundamental underlying disorder in the brain that was activated by hypoglycemia. It fits with Romano's patient who had fundamental personality changes that were not altered after removal of his adenoma. However, he stopped having the epileptic attacks after operation.

Dr. Schwab: Would the original disease be the cause of the seizures indirectly? People who have hypoglycemia usually do not have convulsions, but they do faint and fall and such falls may damage the brain and produce scars. The scars then cause the seizures. I do not know whether we have an answer to this speculation.

Dr. Benjamin Castleman: Following operation she had more attacks. She had one on the ninth postoperative day and one on the tenth.

DR. CHAPMAN: And so she had two diseases.

DR. COPE: That is the question that Dr. Schwab brings up: whether or not one disease gave rise to another.

DR. CASTLEMAN: At autopsy. . . .

DR. CHAPMAN: At autopsy! I thought they cured her.

DR. CASTLEMAN: We were kind enough not to inform you of that.

She was operated on in April of this year and just died a few months ago. We were unable to find anything grossly in the brain to account for the epileptic attacks. On the other hand, we did find something more. She had a large thyroid tumor that was very hard, measured about 10 by 8 by 4 cm. and extended down into the mediastinum to about 3 cm. above the arch of the aorta. She was very obese, and that is probably why the tumor could not be felt. Microscopically it was a very anaplastic tumor with giant cells and in places looked like a fibrosarcoma. It is the type of malignant lesion that is often called carcinosarcoma — a lesion that is probably primarily epithelial. It had metastasized to the lungs but not to any of the regional lymph nodes.

DR. COPE: I think that I am right in saying that she suffered respiratory distress for forty-eight hours before death and died at home. The respiratory distress was of short duration.

DR. CHAPMAN: Death came rapidly, in other words.

DR. SCHWAB: Is there any microscopical report of the temporal region of the brain?

DR. CASTLEMAN: Yes, but the findings did not differ from other regions of the cerebral cortex. According to Dr. Kubik, there was an increase in astrocytes in the deeper layers of the cortex and in scattered areas in the white matter, but these findings were probably of recent origin. I am afraid we did not disclose any focus to explain the seizures.

DR. SCHWAB: One would not expect the sections to show much unless the dura was involved under the temporal lobe; was there any pigmentation there?

DR. CASTLEMAN: No.

DR. SCHWAB: I would like to comment briefly on the low blood sugar. It does not produce convulsions. It has to be at extremely low levels to produce convulsions with a normal brain. Insulin has recently been tried in the diagnosis of epilepsy. Some people have seizures at a level of 30 mg. and others, at a level of 60 mg. per 100 cc. That is a differential method of diagnosing epilepsy but not a general rule. The low blood sugar does not produce convulsions in normal people.

DR. CHAPMAN: With apologies to the Peter Bent Brigham Hospital, I should relate the following. In 1930 a patient had severe hypoglycemia. She fell, fractured her arm, and came to our Emergency Ward. The fracture was treated and, later, she had another seizure and still another seizure, and finally at the Brigham Hospital, Dr. Pokorny made the proper diagnosis of hypoglycemia. She was explored, and the islet-cell tumor removed. This is the first case of this disorder reported in New England.[2]

DR. CASTLEMAN: In the case under discussion, after the tumor was removed, the blood sugar ranged between 150 and 200 mg. per 100 cc., always above 100 mg., whereas previously it was around 45 mg.

A PHYSICIAN: What did the pancreas show at autopsy?

DR. CASTLEMAN: It was perfectly normal. There was no increase in the number of islets in the remainder of the pancreas either at operation or at autopsy.

DR. SCHWAB: Does this disturbance in the thyroid function intensify the effect of islet-cell tumor in reducing blood sugar?

DR. CHAPMAN: In general, when there is more thyroid hormone, the diabetes is worse.

DR. COPE: It is possible that the thyroid lesion was not palpable at the time of operation on the pancreas; it was rapidly growing and presumably developed within a relatively short time. This poor woman was plagued by both these diseases. I think the thyroid carcinoma was probably not related to the other two.

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CASE 35522

PRESENTATION OF CASE

A thirty-eight-year-old married office worker entered the hospital with a complaint of swelling of the right leg.

For the past several years she had experienced mild swelling of both ankles at the end of the day, more marked after being on her feet for long hours. Ten months prior to admission she began to experience cramps in her right foot at night, apparently waking her and subsiding in five or ten minutes. No change in appearance of the extremity was noted at this time, but later the cramps recurred higher in the leg, the leg became red, and a red "line" appeared on the inner aspect of the thigh. Several months following this episode she was seen in a physician's office. At that time swelling of the right leg was as high as the groin. Pelvic examination revealed a firm, fixed, irregular mass, high on the right in the region of the uterosacral ligament. About five months later, after visiting at least one hospital, where a diagnosis of "idiopathic

lymphedema" was made, she returned to her physician. At this time she was receiving codeine because of the pain. She stated that the swelling decreased when she stayed in bed, and that during her last two menstrual periods the pain and swelling were aggravated. Rectal examination revealed an increase in size of the fixed pelvic mass.

The menstrual history was negative, her periods occurring every twenty-six to twenty-eight days, lasting four days and without pain. She had a history of four miscarriages at two to four months during the past eight years.

At the age of eighteen, six months following an appendectomy, a "tumor of the abdominal wall" was excised. At that time she was told by the surgeon that she would probably be unable to have children.

Physical examination revealed a well developed and well nourished woman. In the midthigh the right leg measured 54 cm., and the left 45 cm.; at the calf the right was 42 cm., and the left 34 cm. The right ankle measured 28 cm., and the left 24.8 cm. On pelvic examination a hard, tender mass was felt high in the pelvis. The rest of the examination was negative.

The blood pressure was 130 systolic, 80 diastolic.

Examination of the blood and urine was negative. A prothrombin time was 22 seconds (normal, 18 seconds). An x-ray film of the chest was normal.

On the day following admission an operation was performed.

Differential Diagnosis

Dr. Irad B. Hardy*: We have here the problem of moderately advanced unilateral lymphedema coming on rather rapidly in a young woman. Of course, we must decide what the pelvic mass was and whether it had any causal relation to the swelling. In the first place, I think we can very quickly rule out the systemic causes of swelling of the legs simply on the basis that this was a unilateral affair, and such conditions as nutritional edema, renal disease, heart disease and hyperthyroidism can be discarded. Also, among the mechanical causes of edema any lesion above the bifurcation of the iliacs can be ruled out because this was a unilateral process.

I suspect all we have in the way of x-ray studies is a chest film. May we see it?

Dr. Stanley Wyman: I do not believe there is anything to add to the record, Dr. Hardy. It appears to be within normal limits.

Dr. Hardy: No intravenous pyelogram?

Dr. Wyman: No.

Dr. Hardy: To review the protocol, there are some things we might point out briefly. For several years this woman had mild swelling in both ankles by the end of the day. I do not believe that is very significant; it is a very common complaint. I doubt if it had much bearing on this particular case.

Ten months before being seen in the hospital she began to have some cramps in her leg and later in her thigh, and finally she noted that the leg was red and that a red line had appeared on the inner aspect of the thigh. There was no mention of any special degree of swelling, and I presume there was none. This may have represented an initial episode of mild cellulitis; possibly the red streak was lymphangitis or superficial thrombophlebitis. At any rate, this redness and streaking were not mentioned again, and I think we can assume, if it was an initial episode of cellulitis and infection, that at least it was not repeated over the following months. Several months later (we do not know how much later or how soon before she came in) she had swelling in the groin, and we again have to assume that the swelling had become progressive. She also had an irregular, firm, fixed pelvic mass.

She was then lost track of and upon returning to her physician, which was just about the time she entered the hospital, she had been taking codeine for the relief of pain, which had apparently developed somewhere along the line. I think that, although swollen legs are certainly uncomfortable, the necessity for codeine is not very common. The usual therapy to relieve the pain associated with simple lymphedema is aspirin, an elastic support or elevation. I suspect that this necessity for codeine may indicate that there was some process going on that was involving the nerves as well as the lymphatic drainage.

We then find that the menstrual cycle was essentially normal but that she had had over a period of eight years several miscarriages in the early months. I wonder whether that means a mechanical obstruction in the pelvis, which prevented full-term pregnancies. However, I am of the opinion that that was not the case and that there was probably a hormonal imbalance that prevented her from going on to full term. Later, the mass in the pelvis was apparently of fairly rapid development and probably did not account for the fact that she had not been able to have full-term pregnancies for as far back as eight years previously.

On admission to the hospital the physical examination, such as we have to go on, shows that she had a moderately diffuse swelling located in the right groin. There is no mention of any marked venous stasis, and no mention of a great deal of induration, pigmentation or dilated veins to suggest a postphlebitic state. There is no mention of any redness or cellulitis, which we would have expected to be present if she had had an inflammatory process going on all this time. Since it is not mentioned, I shall assume that it had not been present. No palpable lymph nodes are recorded.

*Assistant in surgery, Massachusetts General Hospital.

In deciding just what type of lymphedema we are dealing with I will run through very briefly one of the better classifications of lymphedema that might be able to help us. I have picked Dr. E. V. Allen's[1] classification, because I think it is the best and easiest to fit into this picture. He divides unilateral lymphedema into noninflammatory and inflammatory groups. Under the noninflammatory group we have the primary and secondary cases. In the primary cases, we have what he calls lymphedema praecox — lymphedema of unknown etiology that comes on in adolescence, usually in females. There is no known obstruction. The lymph vessels are just not capable of handling things, and a gradual process of fibrosis and further obstruction and swelling develops. There is usually no story of cellulitis or recurrent sepsis to account for it. In addition to the praecox type, there is a congenital type of primary lymphedema. But we can rule that out because this occurred in her thirty-eighth year and there was no previous sign, except a little bit of swelling, which I do not believe was true lymphedema.

Under the secondary type of noninflammatory lymphedema, we have occlusion of the lymph system by malignant growth such as metastatic involvement of lymph nodes, or following eradication of the lymph nodes, such as we frequently see after a radical axillary or groin dissection. The cases that follow x-ray or radium treatments are also in this group.

The second division is the inflammatory group of lymphedema, and here also there are infections in the leg brought on for no apparent cause, there being no obvious focus of entry. The episodes are initiated by chills and fever and other symptoms that we have not seen in this case, and therefore I assume that it does not fit into that group.

In the secondary type of inflammatory lymphedema are the cases associated with venous stasis due to old phlebitis and those in which there is marked venous insufficiency and obvious routes of entry for secondary sepsis. The fungous infections and filariasis are considered to be of this group. Also, there are the cases of lymphedema following severe local injury and trauma.

In reviewing all the groups under the classification, I believe this woman of thirty-eight with rapidly increasing swelling in whom there was no evidence of recurrent chills or fever, no significant findings to suggest venous disease or fungous infection and no local injury, probably fits into the secondary group of noninflammatory cases. There may have been occlusion of the lymph channels and lymph nodes in the pelvis and iliac region that was due probably to some type of malignant tumor. We cannot rule out inflammatory disease itself, but I would think if a lesion of this sort were purely inflammatory and widespread enough to cause that amount of swelling there would have been more reaction such as chills and fever.

From the beginning, it has been my impression that this mass was some kind of retroperitoneal condition rather than a pelvic lesion. The examiners were apparently able to outline a normal ovary, a normal uterus and this mass. The retroperitoneal location does not eliminate an ovarian tumor because the ovary may have been in ectopic position or may have become adherent so that the tumor would invade in that direction and plug the lymphatics; it is very farfetched reasoning. I wonder why the doctor at the time of her second operation, when she was eighteen years old, told her that she would have no children after he had operated on the tumor of the abdominal wall. It is just possible that she had an ovary in the inguinal canal.

Another condition that I have to mention, in spite of the negative abdominal examination, the absence of lymph nodes and the normal chest film, is a localized lymphosarcoma involving the pelvic iliac nodes and causing obstruction to the lymph outflow. Although there were several years between, she had had a considerable amount of surgery, some of it rather extensive, and she could have had interference with lymph structures from postoperative scar formation. This may not have manifested itself for several years. Another possibility is some type of local tumor of the lymph vessels such as lymphangioma. However, I think I will have to say that she probably had a lymphosarcoma of the iliac lymph nodes with obstruction to account for the lymphedema.

Dr. Tracy B. Mallory: Are there any questions or suggestions? Dr. Ulfelder, do you want to tell us the opinion on the wards?

Dr. Howard Ulfelder: The protocol could not make it as obvious as it was to us who saw the patient that this pelvic mass was very suggestive of endometriosis. It lay in the posterior cul-de-sac as far as we could tell and could be easily palpated both by pelvic and by rectal examination, and on combined examination it seemed to lie against the posterior aspect of the cervix and anterior to the rectum. It was my impression on the basis of this examination that this mass was more likely to be endometriosis in the region of the uterosacral ligaments than anything else.

Clinical Diagnosis

Endometriosis.

Dr. Hardy's Diagnoses

Lymphosarcoma of iliac nodes.
Lymphedema.

Anatomical Diagnoses

Endometriosis of pelvis and retroperitoneal tissues.
Endometrial metastasis to iliac lymph node.

Pathological Discussion

Dr. Ulfelder: Dr. Hardy was quite correct in classifying this as a case of noninflammatory, secondary, unilateral lymphedema because that is exactly what she had. She had occlusion of the right external iliac vein by a very firm and fibrous mass intimately connected with the lymph nodes in this area. The only unusual feature of the case, and in my experience it is unique, was the nature of the disease within and outside the lymph nodes, because this was also endometriosis. She had endometriosis of the lymph nodes in the operative area surrounding the external iliac vein. Endometriosis was also present outside the lymph nodes, and at the time of operation it was very easily demonstrable that this was the cause of the difficulty. The peritoneum was opened on this side, and dissection carried down along the vessels. The external iliac artery was adherent posteriorly to it but was not involved in the pathologic process. The ureter was not involved in the disease process. It could easily be separated from the peritoneum but the external iliac vein on the right side was completely surrounded by the diseased tissue and was in turn adherent to the pelvic wall. I was not able, of course, to dissect this out because it was too fixed a process, but I was able to free the vein from the pelvic wall and I obtained a biopsy of the fibrous tissue along the pelvic wall. I was also able to remove a number of lymph nodes in the immediate vicinity. The pelvic tumor was entirely separate. It was an endometrioma of the rectovaginal pouch in the usual position, behind the cervical segment and with the bowel adherent to it.

Dr. Alfred Kranes: Was not the absence of dysmenorrhea quite unusual?

Dr. Ulfelder: Dysmenorrhea is classically the symptom of endometriosis, particularly increasing dysmenorrhea. On the other hand, in any analysis of series of cases in which this diagnosis has been made histologically, it is usually noted that about 40 to 50 per cent of patients have not had pelvic pain; it is not by any means a *sine qua non*.

Dr. Mallory: I have a slide I would like to demonstrate. This is from one of the lymph nodes in the region of the iliac vein, and here one can quite clearly see a gland lined with columnar epithelium. Around it is hemorrhagic stroma of the endometrial type. This gland lies just at the margin of the node and is a very clear-cut focus of endometriosis within the node strongly suggestive of a metastasis. I believe metastasis does occur in this condition infrequently but not extremely rarely. There was recently reported from the Gynecological Clinic at Cornell a series of 5 cases showing metastases of endometriosis to lymph nodes and various places around the pelvis.[2]

There was only one lead in the story as written, and that was the accentuation of symptoms at the time of the menstrual periods. That is a rather flimsy lead, I grant, because so many women have accentuation of every kind of symptom at that time.

Dr. Kranes: Was she relieved of her edema?

Dr. Ulfelder: It is not fair to judge so soon. She was operated on recently, and of course her rest in bed brought about a marked decrease in the edema.

Dr. Mallory: In handling this case you thought that it was necessary to remove both ovaries?

Dr. Ulfelder: Yes, I did, for two reasons. I could not tell grossly that this was endometriosis; although that was my impression, it has never been described as producing this picture. So from a diagnostic point of view, I thought I was dealing with a malignant lesion, with metastasis to that site, or with endometriosis, either one of which in this situation would have demanded removal of all the pelvic organs, including both ovaries.

Dr. Mallory: One can be quite sure that after sterilization, it would not progress, but one cannot be sure how much the fibrosis will regress.

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WISE MEN BEARING GIFTS

THE House of Delegates of the American Medical Association, thereby incurring the disapproval of the *Boston Herald* as expressed editorially on December 11, has voted to levy annual dues of $25 on its members. This new source of revenue, provided for in the by-laws, will supplement the now inadequate income that the Association receives from its publications, and will be used to defray the expenses of its various activities in the interest of better medical care for all.

It would appear that the establishment of these dues is part of the legitimate internal affairs of the Association. When acceptable evidence is brought to light that funds are being improperly or even unwisely used, then it may be hoped that such a friend of the ethical profession of medicine as the *Boston Herald* has been will not withhold its criticism.

To those who are interested in examining all sides of a controversial matter, the constructive activities of the American Medical Association must soon become apparent. Its influence in establishing high standards of medical education and hospital service is a matter of history, and its efforts at maintaining these standards through the Council on Medical Education and Hospitals are part of the record. The Council on Pharmacy and Chemistry is tireless in its positive opposition to "fraud, undesirable secrecy, and objectionable advertising in connection with proprietary medicines." Were the newspapers of the country as truly interested in protecting the health of the public as many of them profess to be, they might have consulted the Council on Pharmacy and Chemistry before accepting some of the full-page advertisements of wonder-working drugs that have recently been flung before the public as an open invitation to self-dosing with insufficiently tested remedies.

The representatives of the Fourth Estate, with conspicuously few exceptions, have done well in holding up the hands of the medical profession, represented by the American Medical Association, in its efforts to protect the public health and its own autonomy by combating compulsory health in-insurance. Many of the Association's friends, however, and all of its enemies, need to know more about its positive and constructive activities.

In addition to the two mentioned above, they need to know about the councils on scientific assembly, foods and nutrition, physical medicine, medical service, industrial health and national emergency medical service. They need to know about the committees on therapeutic trials and scientific research and on rural medical service; the bureaus of medical economic research and health education that the Association maintains.

With a full knowledge of these and many other activities, they will then be in a better position to weigh the charge of "accenting the negative" that has been expressed or implied so frequently in recent months.

Great bodies move slowly, and the American Medical Association, representing the rank and file of one of the most conservative professions in

the world, requires time in which to accept a more dynamic philosophy of service and to alter its course accordingly. Being human, it has made its mistakes; being decently human, it is willing to acknowledge them and try to mend its ways.

It must always be remembered, however, by those who clamor for action, that many of the problems of health and disease and the proper distribution of medical care are quite insoluble until patient study, day by day and month by month and year by year, gradually reveals some of the answers. Even the Alexanders of bureaucracy cannot dissolve these knotty problems simply by cutting them.

So far the best answer to the distribution of medical service appears to lie in the voluntary health insurance plans and the education of the public in the tremendous difficulties, responsibilities and often disappointments, as well as the great achievements, day in and day out, that attend the practice of medicine. These difficulties the doctors themselves are constantly trying to overcome, and are even taxing their own incomes to help in the attempt.

The health protection for all that is being purchased with the funds of the American Medical Association may be considered as the gift of the profession to the people of America.

OLD FARMER'S ALMANAC

THE New Year in New England is fittingly heralded by the appearance of *The Old Farmer's Almanac*, published in Dublin, New Hampshire, and now in its one hundred and fifty-eighth year of continuous publication. Introducing the seasons, the months and the days of the year with astronomical fidelity; forecasting the weather for fifty-two weeks ahead with inflexible accuracy and in the utmost detail; reminding its readers of past events and of present duties, and warning them of seasonal dangers on the same superlatively abbreviated pages, the *Almanac* in its familiar yellow cover still holds its place of esteem in those households that recognize man's dependence on the soil.

From these pages it may be learned that bloomers, as an article of female attire, were introduced to an eagerly expectant populace on January 2, 1849, and that January 2, 1950, will be a very cold day; that in the middle of the month the danger of chimney fires is imminent and that on January 24, to be marked by a thaw in 1950, the Chilean earthquake occurred in 1939.

It is the homely traditions of New England, of which the *Almanac* is a tough and persistent symbol, that bind these states together as by a blood relationship. Its fisheries, its forests and its shipbuilding contributed to the early development of New England, and its superb waterpower made it one of the important industrial sections of the country; but it was the New England farm that gave New England its characteristic atmosphere.

The rugged, all-purpose New England farm, where the sheeps' noses had sometimes to be trimmed down on a grindstone before they could get the grass between the boulders, represented not a cash business but a way of life. It was a way of life filled with hard work, but also with certain amenities, the recollection of which has been preserved by John Greenleaf Whittier, a New England farm boy, and by Robert Frost. It was a way of life that is responsible for a nostalgic sympathy with what *The Old Farmer's Almanac* represents, and for an independence of mind and an individual endurance that make New England still a stronghold of democracy and free enterprise.

"BUT FEAR ITSELF"

THE reassurance once issued to the American people by their president that they had nothing to fear "but fear itself" would not suit every occasion, appropriate as it might have been at that time. There are reasonable fears and unreasonable fears, healthy fears and unhealthy ones.

It is with the latter that Terhune* is concerned in discussing his experiences with a group of patients suffering from the "phobic syndrome." This group, comprising 86 persons, represented 2.5 per cent of his psychoneurotic patients. Women in the group outnumbered the men two to one. They were mostly under forty years of age and though

*Terhune, W. B. Phobic syndrome: study of eighty-six patients with phobic reactions. *Arch. Neurol. & Psychiat.* 62:162-172, 1949.

outstandingly intelligent and from financially secure families were only moderately successful, chiefly because handicapped by fear.

These patients were, on the whole, anxious, dependent, emotionally immature young adults who were trying to realize their ambitions and become self-reliant, successful members of society. They were physically healthy, though soft. Reassuring and of prognostic importance is the fact that none of the 86 ever acquired a psychosis. They did have, however, cyclothymic tendencies and "hyperactive vegetative nervous systems that cause unpleasant symptoms which they do not understand and which then give rise to further fear." They were suggestible, imaginative, sensitive persons, with considerable drive, high standards of conduct, active intelligence and ambition. Fearful of situations that might bring on unconquerable panics within them, their instinct for escape was strong. As the author astutely puts it, "They refuse to enter any place from which they cannot escape quickly and with dignity."

A person with a strongly developed anxiety reaction betraying itself in phobic form may be pitiable indeed. He will not or cannot attend parties or enter any public place. Fearing the somatic avalanche of "faintness, weakness, fatigue, palpitation, perspiration, nausea, tremor and difficulty in breathing" that overwhelms him when he finds himself conspicuous in his inadequacy, he dreads equally the crowded theater and the quiet, but peopled church, the city sidewalk whose crowds he has to face alone and the lonely country road that aggravates his sense of insecurity. He fears the high bridge, the water-girt island and the tunnel, from which there seem to be no escape.

It is not difficult to understand that emotional immaturity must be the basis of such unreasoning phobia — that the phobic person, finding himself unable to cope with the apparently dangerous realities of existence, suffers frustrations, becomes "unfavorably conditioned to specific situations," and retreats to a childish level of adjustment. Consciously he may realize that "there is nothing to fear but fear itself," but what a devastating fear that may become!

The phobic patients representing only 2.5 per cent of the psychoneurotic persons that Terhune has encountered, emphasize by their relatively small numbers the varieties of adjustments that human kind must make, the majority of them having as their basis immaturity of emotional development. Few people there must be, indeed, who regularly enjoy complete emotional maturity. With or without specific phobias, emotional immaturity must account for a great deal of the failure and unhappiness in the world; particularly in environments so complicated that full maturity is almost indispensable if they are to be coped with successfully.

The hopeful part of Terhune's paper deals with the apparent success that has rewarded the treatment of the phobias by giving the patient an understanding of his difficulties, socializing him, building up his confidence in himself and reconditioning his fears. By these processes 67 per cent of the group have been permanently relieved of their apprehensions, 24 per cent have been greatly improved to the point where they can work and live efficiently, and only 9 per cent have shown little or no improvement.

Most effective and most efficient of the conditioning mechanisms, however, must be the prevention of these personality disorders. The present road and the road ahead are too rough to be trod barefoot. If the world's children are to overcome the difficulties that the world presents, they must be conditioned to them from the start.

DR. FISHBEIN RETIRES

THE resignation of Dr. Morris Fishbein as editor of the *Journal of the American Medical Association*, after his service of twenty-five years in that capacity, has been accepted by the board of trustees.

During much of this period Dr. Fishbein has been a prominent figure on the American scene, considered by many as the standard-bearer of organized medicine. Physically and intellectually tireless, Dr. Fishbein early assumed an unofficial leadership in the affairs of the Association that went apparently unchallenged until recent years.

As he leaves the headquarters of the Association, possibly with his energetic tongue held temporarily in his cheek, there remain behind him unquestioned monuments to his vigor and sagacity — the *Journal* and the other publications of the American Medical Association and the real contributions that he has made toward raising the standards of medical practice.

Mr. Davis, the man of revelations, is said to be preparing an extraordinary work on medicine, the result of recent interviews with Galen! He was in Boston last week, but whether he met with Galen or Hippocrates here, has not been divulged.

Boston M. & S. J., *December 26, 1849*

Fourth-year students in approved medical schools are reminded of the *Journal's* prize essay competition on "Recent Advances in the Recognition, Treatment and Control of Poliomyelitis."

For further information see *The New England Journal of Medicine*, September 29, 1949, p. 506, or write to the editor.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR NOVEMBER, 1949

RÉSUMÉ

Diseases	November 1949	November 1948	Seven-Year Median
Chancroid	4	5	2*
Chicken pox	927	1740	969
Diphtheria	22	37	28
Dog bite	751	789	620
Dysentery, bacillary	8	3	21
German measles	33	59	60
Gonorrhea	206	262	378
Granuloma inguinale	0	0	0*
Lymphogranuloma venereum	0	1	1*
Malaria	1	1	15
Measles	141	2790	691
Meningitis, meningococcal	3	2	7
Meningitis, Pfeiffer-bacillus	4	4	5
Meningitis, pneumococcal	2	5	4
Meningitis, staphylococcal	0	0	0
Meningitis, streptococcal	1	0	0
Meningitis, undetermined	10	3	3
Mumps	385	1021	523
Poliomyelitis	76	5	24
Salmonellosis	3	3	7
Scarlet fever	236	465	466
Syphilis	133	183	391
Tuberculosis, pulmonary	196	232	220
Tuberculosis, other forms	7	18	12
Typhoid fever	3	1	1
Undulant fever	1	2	4
Whooping cough	539	254	598

*Five-year median.

COMMENT

This month dog bite, poliomyelitis and typhoid fever were above the seven-year median.

Diseases below the seven-year median were German measles, measles, mumps and scarlet fever.

There were 751 cases of dog bite this month, which was second only to November, 1948, when there were 789 cases.

Poliomyelitis continued to decline steadily from the high level of August, with 76 cases this month compared to a seven-year median of 24 cases.

Scarlet fever was at the lowest incidence ever recorded in November. Measles was at the lowest since 1907, and German measles at the lowest in ten years.

The incidence of whooping cough is rising, being at the highest level since December, 1947.

GEOGRAPHICAL DISTRIBUTION OF CERTAIN DISEASES

Diphtheria was reported from: Ayer, 1; Boston, 12; Leominster, 1; Malden, 1; Somerville, 6; Wilmington, 1; total, 22.

Dysentery, bacillary, was reported from: Boston, 4; Brookline, 1; Cambridge, 1; Somerville, 1; Worcester, 1; total, 8.

Encephalitis, infectious, was reported from: Lynn, 1; Mansfield, 1; Palmer, 1; Springfield, 1; total, 4.

Infectious hepatitis was reported from: Revere, 1; total, 1.

Malaria was reported from: Northampton, 1; total, 1.

Meningitis, meningococcal, was reported from: Boston, 1; Salem, 1; Springfield, 1; total, 3.

Meningitis, Pfeiffer-bacillus, was reported from: Belmont, 1; Brockton, 2; Holyoke, 1; total, 4.

Meningitis, pneumococcal, was reported from: Needham, 1; Worcester, 1; total, 2.

Meningitis, streptococcal, was reported from: Ashland, 1; total, 1.

Meningitis, undetermined, was reported from: Danvers, 1; Fall River, 2; Greenfield, 1; Longmeadow, 1; Lowell, 1; Needham, 1; South Hadley, 1; Spencer, 1; Woburn, 1; total, 10.

Poliomyelitis was reported from: Ashburnham, 1; Attleboro, 1; Boston, 7; Bourne, 1; Brookline, 1; Cambridge, 3; Chelmsford, 2; Concord, 3; Dedham, 1; Dracut, 2; Fitchburg, 1; Greenfield, 1; Hamilton, 1; Hingham, 1; Holliston, 1; Hopedale, 1; Lee, 1; Lexington, 1; Lincoln, 1; Longmeadow, 1; Lowell, 4; Marion, 1; Marshfield, 1; Medford, 2; Milton, 1; Nahant, 1; Natick, 1; Needham, 1; New Bedford, 1; Newton, 2; North Attleboro, 1; Norwell, 1; Oakham, 1; Orange, 1; Palmer, 1; Pittsfield, 1; Quincy, 1; Saugus, 1; Somerset, 1; Taunton, 1; Tyngsboro, 1; Waltham, 6; Wellesley, 1; Weston, 1; West Springfield, 1; Winchester, 1; Worcester, 6; Wrentham, 1; Plymouth, 1; total, 76.

Salmonellosis was reported from: Cambridge, 1; Fall River, 1; Norwood, 1; total, 3.

Septic sore throat was reported from: Boston, 2; Braintree, 1; Fall River, 1; Worcester, 1; total, 5.

Tetanus was reported from: Gloucester, 1; Pittsfield, 1; total, 2.

Typhoid fever was reported from: Brookline, 1; Ipswich, 1; Plymouth, 1; total, 3.

Undulant fever was reported from: North Adams, 1; total, 1.

CORRESPONDENCE

LAISSEZ FAIRE

To the Editor: Although inactivated myself from the practice of medicine and conscious of a consequent inability to sense the emotions of the man who is in active practice, I feel moved to protest these twenty-five dollar assessments, which seem on the way to becoming a permanent medical liability.

In making this protest may I state that I have no sympathy for the compulsory insurance program but I should like to observe that opposition to the program and contributions to make this opposition effective are by no means the exclusive responsibility of physicians. Physicians will be hurt no more than the average citizen. There is nothing to indicate that a physician's income will be seriously less than at present though his satisfactions and his morale stand to be lowered through loss of incentive. There is reason to predict a dismal future for scientific achievement in the field of medicine. The results of these changes will be felt by the average citizen in higher taxes and a distinct loss in the standards of individual consideration that he now expects from his physician.

Now that the A. M. A. has spent its millions in its educational campaign this year, making these facts clear to the nation, if the majority still wish to have Government hand-

outs, Government bankruptcy and socialized medicine — if they wish to have a look at the inside of a bog — I say, "Let 'em."

I am willing to contribute to a campaign waged by people of all trades and professions but I will not willingly contribute to a fund raised solely by physicians.

ALLAN R. CUNNINGHAM, M.D.
Winchester, Massachusetts

BOOK REVIEWS

Practical Lessons in Psychiatry. By Joseph L. Fetterman, M.D. 8°, cloth, 342 pp. Springfield, Illinois: Charles C Thomas, 1949. $5.75.

The author, who has been an executive officer of the School of Military Neuropsychiatry, wrote this book as an outgrowth of lectures at this school and of seminars given in Cleveland. A wealth of material is presented in concentrated form, arising from the author's military and civilian experience. The lively style, together with the very numerous examples, makes this book pleasant reading.

In the introductory chapter on the patient and his personality the author shows that learning never should exclude common sense. Psychoneuroses and their treatment are given rather thorough consideration. The possibilities of "short psychotherapy" are discussed and illustrated by histories. The author expresses his opinion concerning disputed questions and attempts to formulate new interpretations. For instance, he emphasizes the organic factors in the etiology of endogenous depression, and in schizophrenia he adds to the usual types the subdivision of schizoaffective disorders. This last group runs a cyclic course and responds well to shock therapy. The author states, "Those cases which fail to respond and ultimately require confinement to state hospitals are usually true Schizophrenias." The book deals thoroughly with insulin and "electro-coma therapy," which are best suited to the affective disorders. His own working hypothesis is that the mood is cyclic and tends to return to the baseline of average normality. This tendency is also present in manic-depressive states in which the cycle may take a year or more. Electrocoma therapy accelerates this tendency to return to the average state. "The passage of the current through the brain and the convulsion effect the physiological. . .change which proves to be both a stimulus to improve bodily function and a removal of self-attacking mechanisms!" In schizophrenia "this restoration of the mood towards normal may carry with it a change in ideation."

The book deals with all manifestations of mental disorders, and much consideration is given to the military, industrial, legal and social aspects. Dr. Fetterman says in the preface that he planned this book for general practitioners, nurses, psychologists, personnel advisers and social workers, but, the psychiatrist, too, will appreciate many of the opinions, which are borne out by the author's great experience.

Pathology and Surgery of Thyroid Disease. By Joseph L. DeCourcy, M.D., and Cornelius B. DeCourcy, M.D. 8°, cloth, 476 pp., with 93 illustrations. Springfield, Illinois: Charles C Thomas, 1949. $10.00.

Recent developments in the treatment of thyroid disease have been unusual. The utilization of ever-increasing varieties of antithyroid drugs and of radioactive iodine in the study and treatment of certain affections of the thyroid gland has been responsible, in a measure, for the publication of several new textbooks relating to the general subject of thyroid disease. This volume brings still another shade of opinion to bear on this, as ever, controversial subject.

These authors, in presenting their convictions in this regard, draw heavily upon their large personal experience in the surgical treatment of thyroid disease. These convictions, in the main, are conventional, and are attested to by the cumulative experience of other recognized authorities in the field.

This treatise, consisting of 476 pages with 93 illustrations, is divided into sixteen chapters. The chapters concerned with the anatomy, embryology, physiology and pharmacology of the thyroid gland are adequate in terms of thoroughness and accuracy. The description of the clinical features of the various diseases of the thyroid gland is well done. In certain aspects, however, the position of the authors is more novel, and therefore will be subjected to some questioning in quarters having a comparably large experience with the management of thyroid disease.

It is essentially in the field of therapy that significant differences in points of view will be manifest.

The authors apparently consider iodine (Lugol's solution) as the treatment of choice in the preoperative preparation of the average thyrotoxic patient for thyroidectomy, although they cover, with ample discussion and thorough documentation, the historical development and clinical application of the various thiourea derivatives in the preoperative management of thyrotoxic patients. The authors utilize certain thiourea drugs in conjunction with iodine in the preparation of selected patients with diffuse toxic goiter for thyroidectomy. They state specifically (p. 214), however, that "toxic nodular goiter should not be treated with thiouracil, but should (also) be removed surgically." It is not entirely clear to the reviewer whether the authors mean to say that patients with toxic nodular goiters should not be given thiouracil even as a preliminary adjunct to subsequent thyroidectomy or whether they are merely opposed to its utilization as a substitute for surgery. In the opinion of the reviewer, based upon the experience of the Lahey Clinic, propylthiouracil is currently the preparation of choice in the preliminary restoration of normal metabolism in the presence of either diffuse or nodular toxic goiter. Iodine, in the form of Lugol's solution, is employed during the last two or three weeks of thiouracil therapy to induce involution of the hyperplastic gland in the patient with primary hyperthyroidism (diffuse toxic goiter). No iodine is used routinely in the nodular toxic goiters.

The reviewer is in thorough agreement with the authors in their convictions regarding the necessity of treating patients with diffuse and nodular toxic goiters by subtotal thyroidectomy and the importance of iodine in conjunction with thiourea derivatives in the preparation of patients with diffuse toxic goiter (primary hyperthyroidism) for surgery, and is in opposition to the thesis that radioactive iodine will replace surgery in the treatment of thyrotoxicosis.

DeCourcy and DeCourcy advocate routinely the use of small doses of thyroid extract postoperatively for a period of approximately a year in all cases of hyperthyroidism. They base this advocacy on the theory that "by keeping sufficient thyroid in the blood stream following operation, the thyroid remains at rest." They believe that their low incidence of recurrent hyperthyroidism is due, in some measure, to this practice. Some surgeons and internists, with wide experience in the treatment of thyroid disease, will question the validity of this contention, and will believe that the authors' low rate of recurrent hyperthyroidism following subtotal thyroidectomy is probably due to the thoroughness with which the operation is performed. Many will fear the routine use of thyroid extract after operation because of the conviction that, in certain cases, thyrotoxicosis apparently has been induced by its injudicious administration. One might also point out the theoretical possibility that the concentration of iodine in thyroid extract could be responsible for any therapeutic benefit that might derive from the administration of desiccated thyroid in this connection.

In performing thyroidectomy, the authors do not routinely divide the strap muscles, expose the recurrent laryngeal nerve, demonstrate the parathyroid glands or ligate the inferior thyroid artery — technical considerations that are believed to add to the safety of the operation.

This book is well organized, generously illustrated and carefully documented. To this increasingly controversial field of medical and surgical therapy it brings considerable support to certain conventional concepts, and novel convictions in some regards, which may tend to widen the area of conflicting opinion.

Cardiovascular Disease: Fundamentals, differential diagnosis, prognosis and treatment. By Louis H. Sigler, M.D. 8°, cloth, 551 pp., with 149 illustrations. New York: Grune and Stratton, 1949. $10.00.

At present, refresher courses for physicians are in the curriculum of practically every teaching institution. Here is a book that would serve well as a refresher course in cardiovascular diseases. It covers briefly the fundamentals, differential diagnosis and prognosis of heart disease. Another

valuable point is the view of the author, who looks upon disease as a unit affecting the entire organism even though limited clinically to localized structures and organs.

The book covers practically the entire field of cardiology. It starts with a chapter on the general incidence of cardiovascular disease and runs through the whole gamut including congenital heart disease and psychosomatic cardiovascular abnormalities and contains a final chapter on surgery and cardiovascular disease. This book also has a number of very informative illustrations and is well documented. There is, however, one fundamental fault: in some places the author is too brief, and important other subjects are completely omitted. For example, electrocardiography, which is essential in heart disease, is covered in only one paragraph—giving a reference to an article that covers the subject. At least one chapter should have been devoted to this subject.

The reviewer found it a very profitable book that briefly covers most of the essentials in the field of cardiology.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

From Thirty Years with Freud. By Theodor Reik. Translated by Richard Winston. Second printing. 8°, cloth, 241 pp. New York: International Universities Press, Incorporated, 1949. $3.75.

This volume is a second printing of a book first published in 1940. The material is divided into four parts: Freud and his followers, including biographic material on Freud; an unknown lecture of Freud's; Freud as a critic of culture; and essays on diverse subjects. To those not owning the 1940 original this reprint presents the opportunity of procuring this work on psychoanalysis.

Conference on Metabolic Aspects of Convalescence. Transactions of the Sixteenth Meeting, New York, New York, October 27-28, 1947. 8°, cloth, 168 pp., with 39 illustrations. $3.00. *Transactions of the Seventeenth Meeting, New York, New York, March 29-30, 1948.* 8°, cloth, 246 pp., with 79 illustrations. $4.00. Edited by Edward C. Reifenstein, Jr., M.D. New York: Josiah Macy, Jr., Foundation, 1948.

In both these conferences a number of papers were presented on the adrenocorticotropic hormone and adrenal conditions and on protein metabolism. Detailed tables of contents take the place of indexes. The volumes should be in all medical libraries and available to all research workers in the field of metabolism.

Obesity. By Edward H. Rynearson, M.D., Division of Medicine, Mayo Clinic, and associate professor of medicine, Mayo Foundation; and Clifford F. Gastineau, M.D., fellow in medicine, Mayo Foundation, Rochester, Minnesota. 8°, cloth, 134 pp., with 9 illustrations and 16 tables. Springfield, Illinois: Charles C Thomas, 1949. $3.50.

This monograph, prepared for the practicing physician, considers the various aspects of obesity. The introduction presents valuable weight tables for men and women of ages twenty-five and over; percentage of overweight and underweight, deaths per 100,000 from all causes and all ages by weight classes; influence of overweight on mortality in persons aged forty-five to fifty years; and the influence of body weight on mortality. In order the physiology, etiology, contraindications to reduction and treatment, including diet, psychotherapy, drugs, heat, and exercise and massage, are discussed. The chapter on diets was written by Alice Karslake Irmisch and contains many diet tables. There is a bibliography of 422 easily obtainable references. Surprisingly, there is not an index. The book should be in all medical libraries and should prove useful to the practicing physician.

Facts About the Change of Life. By E. C. Hamblen, M.D., professor of endocrinology and associate professor of obstetrics and gynecology, Duke University School of Medicine, and chief of the endocrine division and endocrinologist, Duke Hospital, Durham, North Carolina. 12°, cloth, 86 pp. Springfield, Illinois: Charles C Thomas, 1949. $2.50.

This small book is written for women and presents in simple language the information that they need concerning the menopause, with the object of dispelling unnecessary fears during this period. The anatomy and physiology of the female sexual organs and the endocrine system, hygiene and the nervous and mental conditions incident to this period are discussed. There is a chapter on cancer in which the author points out that the occurrence of cancer during the menopause is chronologic and casual.

Applied Psychoanalysis: Selected objectives of psychotherapy. By Felix Deutsch, M.D. 12°, cloth, 244 pp. New York: Grune & Stratton, 1949. $3.75.

The Boston Psychoanalytic Society, during the years 1942-1947, conducted a psychiatry clinic for the treatment of neuroses. The knowledge gained during this period is summarized in this small volume. The material is divided into four parts: goal-limited adjustment (sector therapy, with an analysis of two cases, one with fourteen interviews); psychiatry and social work (including psychoanalysis); mental health in industry — job phobia; and family disruption (separation neurosis). A short bibliography is appended to the chapter on mental health in industry. There is a good index. The small volume is well published.

Problems of Early Infancy. Transactions of the Second Conference, March 1-2, 1948, New York, New York. With Supplement Covering Special Meeting, July 18-19, 1947, New York, New York. Edited by Milton J. E. Senn, M.D., departments of pediatrics and psychiatry, Yale University School of Medicine. 8°, cloth, 120 pp. New York: Josiah Macy, Jr., Foundation, 1948. $1.00.

The main themes of this conference were the psychologic problems of pregnancy and neurotic conditions in children in wartime. Eighteen persons delivered papers at the meeting. This volume should be in all medical libraries, as well as all the special conferences sponsored by the Macy Foundation.

Help Yourself to Better Sight. By Margaret D. Corbett, 8°, cloth, 218 pp. New York: Prentice-Hall, Incorporated, 1949. $2.50.

In this volume, written for the laity, the author describes the Bates method of relaxation for rebuilding vision in defective eyes.

Outwitting Your Years. By Clarence W. Lieb, M.A., M.D. 12°, cloth, 278 pp. New York: Prentice-Hall, Incorporated, 1949. $2.75.

This popular book, written for persons in their fifties and over, discusses hygiene, work, exercise, hobbies, and the so-called diseases of old age, including heart disease, high blood pressure and cancer. It is pointed out that cancer is not part of the aging process but is prevalent in women of forty to sixty and in men over sixty. Also, the painful condition of arthritis is considered. The text is well written in a simple manner and abounds with common-sense advice.

Public Health Statistics. By Marguerite F. Hall, M.A., Ph.D., associate professor of public-health statistics, School of Public Health, University of Michigan. Second edition, revised. 8°, cloth, 441 pp., with 41 illustrations. New York: Paul B. Hoeber, Incorporated. 1949. $7.50.

In this revision of a special work, part of the text has been rewritten and the material brought up to date. The statistical tables have been revised, and some tables have been added. There is a new chapter, illustrating three of the most useful applications of life-table technics to the materials available in public-health activities. A section has been added to the chapter on correlation to give greater emphasis to correlation technic. Likewise, the author has attempted to simplify the basic theory of the application of the normal curve to statistical processing of public-health data. Much of the material in the original chapter on estimates of popula-

tion has been deleted as obsolete because of the new technics originating with World War II. The section on sampling emphasizes three variables that must be known before the size of the sample can be determined. The publishing is excellent. The book should be in all large public libraries and in all collections on public health and statistics.

Textbook of Medicine. By various authors. Edited by Sir John Conybeare, K.B.E., M.C., D.M. (Oxon.), F.R.C.P., physician to Guy's Hospital, London. Ninth edition. 8°, cloth, 875 pp., with 28 illustrations. Baltimore: Williams and Wilkins Company, 1949. $8.00.

This composite textbook, the work of eighteen British physicians, was first published in 1929. Its long life is good evidence of its soundness and popularity. The volume is well published. The paper, type and printing are excellent. There is a good index. The printing was done in Great Britain. The work should be in all the large medical libraries.

The American Nurses Dictionary: The definition & pronunciation of terms in the nursing vocabulary. By Alice L. Price, B.S., R.N., instructor of nursing arts at Columbia Hospital, Milwaukee. 12°, cloth, 656 pp. Philadelphia: W. B. Saunders Company, 1949. $3.75.

This new dictionary defines approximately 25,000 words and indicates their pronunciation, a very valuable feature. The text is concluded with a number of tables, including abbreviations, prefixes and suffixes, chemical symbols and elements. The book is well published and should prove generally valuable. It should be in all public and medical libraries.

Vocabulary Guide: A teacher's supplement to the American Nurses Dictionary. 8°, cloth, 101 pp. Philadelphia: W. B. Saunders Company, 1949.

The separate supplement is designed for nurses and is arranged topically.

NOTICES

SPRINGFIELD HOSPITAL CONFERENCES

The following conferences will be held at the Springfield Hospital, Springfield, Massachusetts, during January, 1950:

Saturday, January 7, 12 noon. Symposium on Diseases of the Thyroid Gland.
I. Diagnosis and Treatment of Simple Goiter and Inflammatory Diseases of the Thyroid Gland. (Staff Conference Room.)

Saturday, January 14, 12 noon. Symposium on Diseases of the Thyroid Gland.
II. Diagnosis and Treatment of Graves's Disease. (Staff Conference Room.)

Tuesday, January 17, 8:30 p.m. Clinical Pathological Conference. (Staff Conference Room.)

Saturday, January 21, at 11:00 a.m. Springfield Hospital Guest Speaker Conference. Dr. Samuel Levine, Boston. Topic: "Auscultation of the Heart."

Saturday, January 28, 12 noon. Symposium on Diseases of the Thyroid Gland.
III. a. Diagnosis and Treatment of Thyroid Neoplasms.
b. Complications following Therapy of Thyroid Disease.

Conferences are open to all interested physicians.

NEW ENGLAND CARDIOVASCULAR SOCIETY

A meeting of the New England Cardiovascular Society (formerly, the New England Heart Association) will be held in the amphitheater of the Dowling Building, Boston City Hospital, on Monday, January 9, at 8:00 p.m., Dr. Laurence B. Ellis presiding.

PROGRAM

The Use of an Oral Mercurial Diuretic in Ambulatory Patients. Drs. Elliot Bresnick, Julius Abramson and Peter L. Sapienza.

Khellin in the Treatment of Angina Pectoris. Drs. Harold Osher and Kermit H. Katz.

The Effect of Intravenous Digoxin on the Dynamics of the Circulation in Congestive Heart Failure. Drs. Richard A. Bloomfield, Garth K. Graham, Henry Kraus and Paul H. Pfeiffer.

The Effect of Digitalis on the Oxygen Consumption, Ventilation and Pulse Rate during Exercise in Normal Subjects and Patients with Heart Disease. Drs. Herbert S. Sise and Kenneth Chesky.

Evaluation of Surgical Treatment of Angina Pectoris. Drs. Dwight E. Harken, Robert C. Farrand and Leon R. Norman.

The Use of Cation-Exchange Resins in Patients with Cardiac Edema: A preliminary report. Dr. Henry Kraus.

Interested physicians and medical students are cordially invited to attend.

AMERICAN COLLEGE OF ALLERGISTS

The sixth annual congress of the American College of Allergists will be held at the New Hotel Jefferson, St. Louis, Missouri, January 15 through 18. The subjects of allergy of the eye, dangers of cosmetics, snake venom in the treatment of urticaria, shortening the treatment of hay fever, allergy in France, England and Ireland, relation of allergy to character problems in children, marital adjustments of parents of allergic children and many others will be discussed. Dr. Paul Kallos, of Helsingborg, Sweden, will be awarded the von Pirquet medal for outstanding achievement in allergy.

BOSTON HEALTH DEPARTMENT EXAMINATIONS FOR TUBERCULOSIS

Gastric examinations for tuberculosis may be obtained by appointment on Mondays, Wednesdays and Thursdays at the laboratory of the Boston Health Department, Haymarket Square (Telephone, CA 7-1300). Examinations may be obtained for their patients by all physicians, but the patients must live in Boston.

VETERANS ADMINISTRATION RESIDENCY TRAINING IN NEUROPSYCHIATRY

A limited number of openings are available for July 1, 1950, appointment to the Veterans Administration residency training program in neuropsychiatry. This program is under the jurisdiction of the deans of the Boston medical schools (Harvard, Tufts and Boston University). Training in this program, which may be from one to three years, is given at the following institutions:

Cushing Veterans Administration Hospital, Framingham, Massachusetts.
Bedford Veterans Administration Hospital, Bedford, Massachusetts.
The Mental Hygiene Clinic of Boston, Regional Office of Veterans Administration, Boston, Massachusetts.
West Roxbury Veterans Administration Hospital, West Roxbury, Massachusetts.
White River Junction Veterans Administration Hospital, White River Junction, Vermont.

Emphasis in the entire program is on psychiatry with dynamic orientation and includes closed-ward, open-ward, outpatient and child psychiatry and neurology. Training in child psychiatry is given at the Children's Medical Center, Massachusetts General Hospital and Habit Clinic, Boston.

All stations are within commuting distance of the Boston Psychoanalytic Institute, in the event that applicants have been accepted for analytic training.

Further information may be obtained from Dr. J. L. Hoffman, chief, Professional Services, Bedford Veterans Administration Hospital, Bedford, Massachusetts, or from Dr. Wilfred Bloomberg, chief, Neuropsychiatric Service, Cushing Veterans Administration Hospital, Framingham, Massachusetts.

(*Notices concluded on page ix*)